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SENSORY PATHWAYS OF THE OVARIAN PLEXUS*

AN EXPERIMENTAL STUDY

JOHN S. LABATE, M.D., AND SAMUEL R. M. REYNOLDS, PH.D.,
BROOKLYN, N. Y.

(From the Department of Obstetrics and Gynecology, New York University College of Medicine, and the Department of Physiology, Long Island College of Medicine)

THE purpose of the present study was to determine the segmental distribution of the sensory pathways from the ovarian plexus to the central nervous system.

Such an investigation should provide a basis for interpretation of various reflex phenomena (viscerosensory and visceromotor) which are associated with certain pathologic conditions of some of the abdominal and pelvic organs. Moreover, exact knowledge of the distribution of the different fibers may facilitate more precise and less extensive surgical procedures for the relief of pain when such steps are indicated.

In addition, studies of this type should provide a logical approach to the study of the normal functions subserved by the many sensory connections from the female genital tract. If the chief morphologic features of these pathways, motor as well as sensory, are known, stimulation or destruction of selected reflex arcs will be possible. By such procedures the rôle of the innervation of the female genital tract may be ascertained without resorting to extensive and unnecessary sympathectomy. The extensive sympathectomies so far employed may

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result in a physiologically abnormal animal, and they have yielded no tangible results which reveal the functions of the abundant innervation of the uterus, tubes, and ovaries.

The method employed in this study is based on the well-known stimulating effect on respiration and blood pressure, resulting from electrical stimulation of peripheral sensory nerves. A number of recent investigators have utilized this method to study sensory effects from certain viscera. Thus Shrager and Ivy (1928) and Davis and others (1932) showed that when the gallbladder of a cat is distended certain reflex effects, such as increased respiratory movements, salivation, and distress, occur. Likewise, Acheson and others (1936) presented evidence to show that the contraction of the nictitating membranes, an increase in blood pressure, respiration and heart rate result reflexly from stimulation of sensory somatic or autonomic nerves whose central connections are intact.

In the present experiments we also have utilized the increase in blood pressure and respiratory movements resulting from strong faradic stimulation of various components of the ovarian plexus and the absence of such effects when essential pathways have been severed. By appropriate application of these procedures, which are given in detail below, we have investigated (1) the origin of the afferent fibers of the ovarian plexus; (2) the course of the sensory components; and (3) their central distribution within the main ganglionated sympathetic trunk.

METHODS

Animals.—Nine cats were used in this study. In seven, sensory nerves from both ovarian plexuses were stimulated. Thus a total of sixteen ovarian plexuses were studied.

Five of the animals, two of which were near term, were pregnant. Three cats were nonpregnant and one was in a postpartum state with good involution. In the latter animal a number of small follicles were present in the ovaries. The reproductive states of the cats did not affect the results described below, however.

Anesthesia.—In the first few experiments 0.7 c.c. of dial (Ciba) per kilogram of body weight was used. However, this produced a deep anesthesia which affected adversely the reflex responses to faradic stimulation. Later we found that 0.4 c.c. per kilogram maintained the animal in light anesthesia without depressing the reflexes to any great extent.

Ether was given by inhalation during the preliminary operative procedures of inserting the carotid cannula and the respiratory trocar and performing laparotomy. The re-enforcement with ether to produce first plane of anesthesia prevented the onset of shock and eliminated movements and distress which later might interfere with normal reflex responses to electrical stimulation.

Recording Technic.—Changes in blood pressure were registered through a carotid cannula. Respiratory movements were recorded by means of a trocar which was plunged into the pleural cavity through the sixth or seventh costal interspace in the anterolateral aspect of the chest. The trocar was connected by a rubber tubing

to a tambour by means of which the kymographic tracings were obtained. This method was simple, produced little trauma and registered minute fluctuations in rate and depth of the respiratory excursions.

A strong faradic current was used for stimulation. After the sensitive area about the ovarian vessels in the broad ligament was found, a shielded electrode was applied at this point. The electrode was tested for freedom from transmission of current to the surrounding tissues and then kept in this position throughout the remainder of the experiment. After several viscerosensory reflex responses were obtained, ablation of any desired portion of the sympathetic nervous system was performed and the effects noted. If, as a result of the ablation, the sensory effects were abolished, the central end of the site of section was then stimulated. By alternate and progressive stimulation, section and stimulation, the essential sensory pathways originating in the ovarian plexus were traced (Figs. 1 to 4).

In a total of 50 observations in which the sensory pathways were intact from the site of stimulation, there occurred an average rise in blood pressure of 13 mm. There was no noticeable effect on the heart rate. The respiratory effect was variable. In some instances there was an increase in depth without a corresponding increase in rate, while in others the opposite occurred. In only four cases was there a decrease in frequency of respiratory movements. In 29 observations an average increase in rate of 9 per minute was noted. In 17 instances no change in rate occurred, but in such cases the depth of respiration usually increased. In 7 no change in depth was noted. In 6 cases the respiratory change was characterized by an initial inspiratory spasm with the onset of stimulation.

RESULTS

I. Peripheral Distribution of Sensory Components of the Ovarian Plexus.—Fig. 1 illustrates the origin and peripheral distribution of the sensory fibers of the ovarian plexus, as revealed by the use of the procedures outlined above.

The ovarian arteries in the cat arise from the abdominal aorta slightly above the level of the fifth lumbar sympathetic ganglion. The vessels course downward and laterally to enter a short fold of peritoneum which anchors the ovary and tube to the side wall of the pelvis. The ovarian vessels enter this suspensory ligament and after a short distance branch peripherally to supply the ovary and tube.

At the outset of the experiments it was deemed necessary to find the point of greatest sensitivity in the ovarian plexus. This was found to be a point on the ovarian vessels within the suspensory ligament just proximal to their point of bifurcation into their peripheral branches (Fig. 1, *A*, *a*, *b*).

Various spots within the broad ligament in the vicinity of the ovarian vessels adjacent to this site were stimulated but no sensory response was elicited. However, when the electrode was placed on the ovarian vessels and a stimulus applied, there resulted marked reflex responses on the blood pressure and respiration. The electrodes

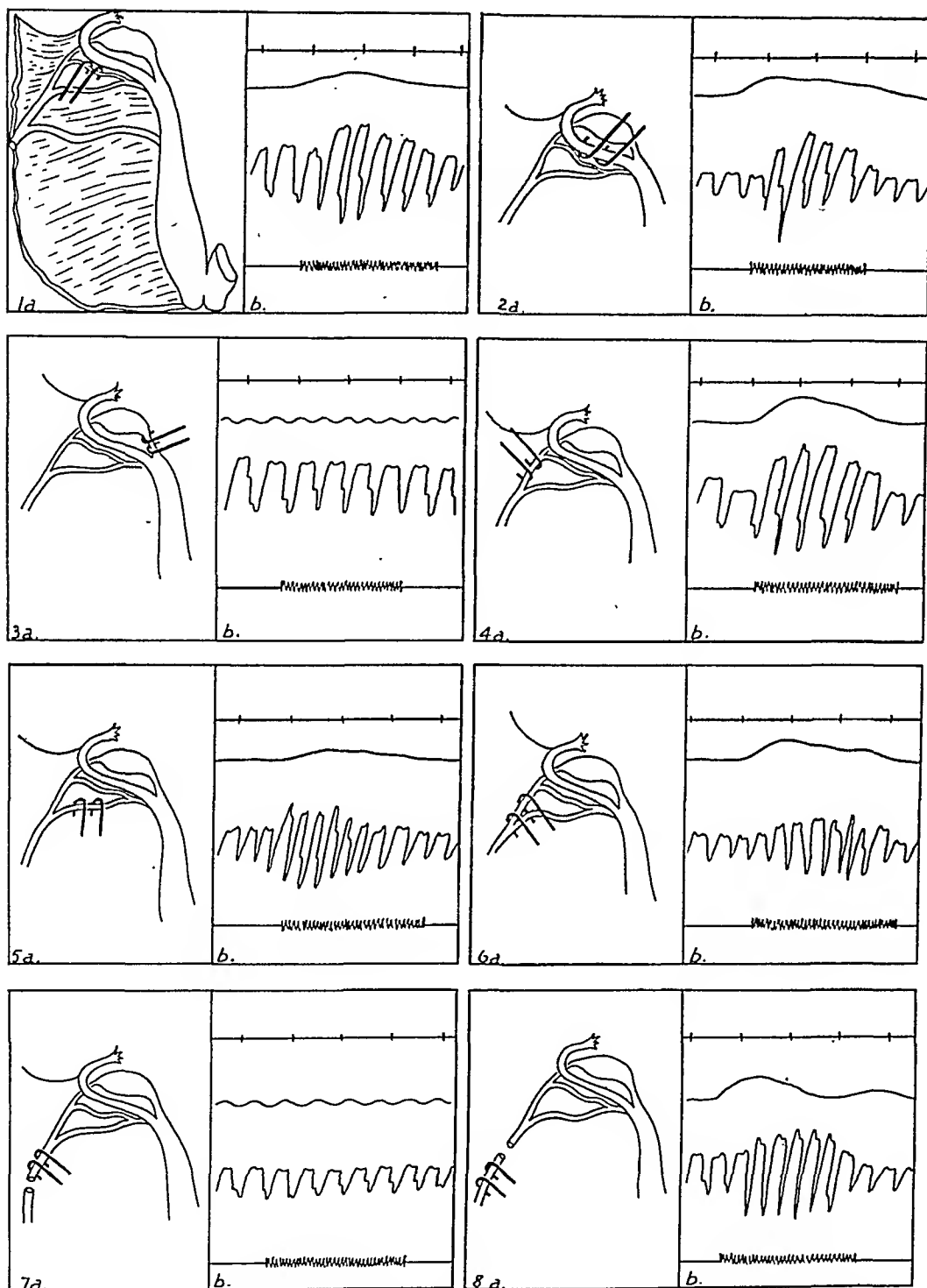


Fig. 1.—Figures showing the peripheral distribution of sensory components of the ovarian plexus. 1, 2, 4, 5 and 6 show sites from which sensory components arise. 3 shows lack of sensory fibers in the ovarian ligament connecting the uterus and ovary. 7 and 8 show that the sensory components noted above all pass along the ovarian artery. Key to this and other figures: *a*, Schematic figures of experimental procedures and sites of stimulation. *b*, Sensory reflex effects on blood pressure and respiratory movements. Top line, five-second intervals; second line, blood pressure; third line, respiratory movements; fourth line, electrical stimulation and zero level for blood pressure. See text for discussion.

were then moved peripherally along the branches of the ovarian vessels with the production of typical reflex effects (Fig. 1, 3*a* to 6*b*).

The ovarian ligament which anchors the ovary to the uterus was found to be devoid of sensory fibers as indicated by failure to obtain reflex effects on electrical stimulation (Fig. 1, 3, *a*, *b*). Stimulation of

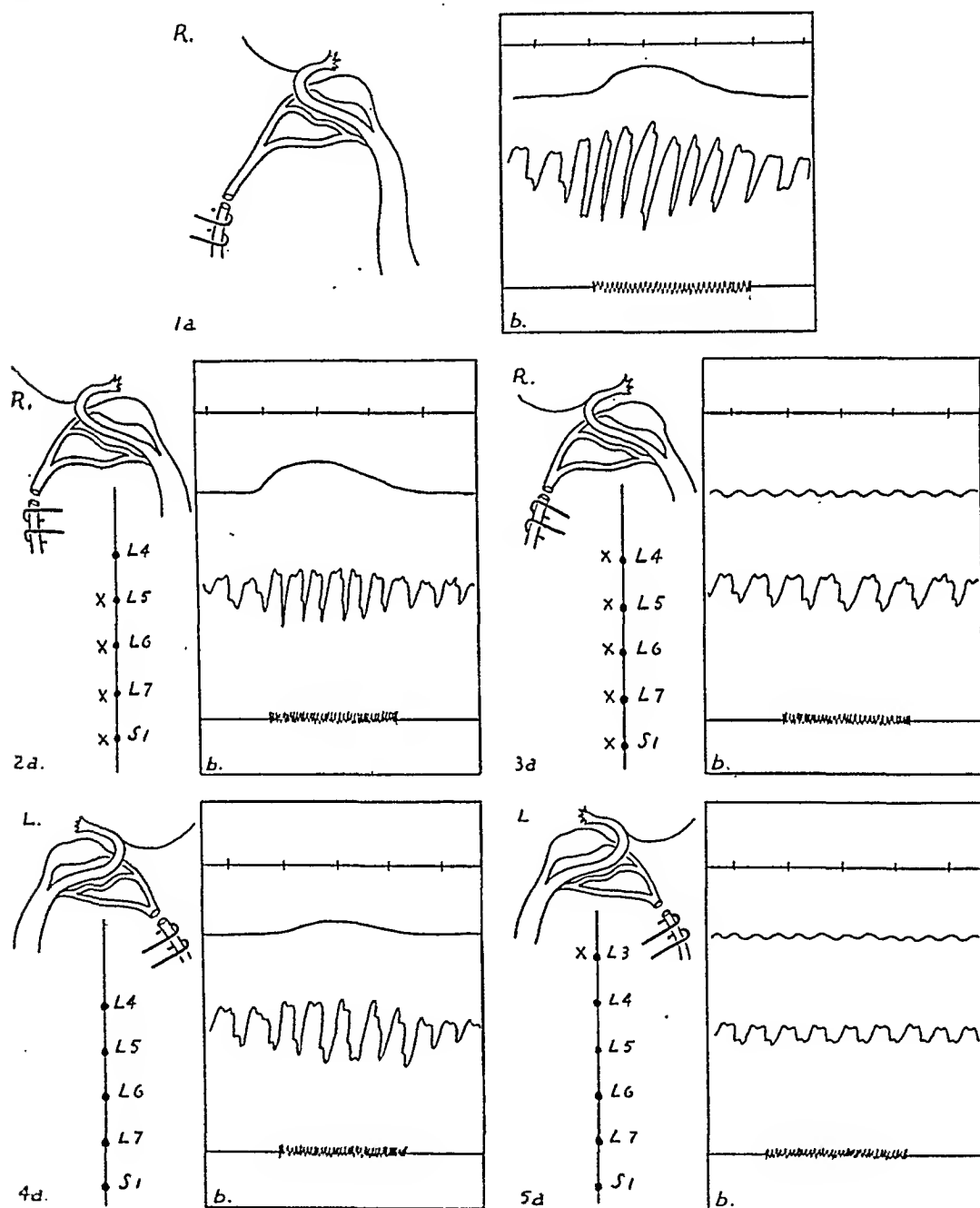


Fig. 2.—Figures showing sensory pathways of ovarian plexus to the main ganglionated sympathetic trunk. 1*a*, *b*, normal responses with stimulation of main sensory pathway from ovarian plexus (see Fig. 1). 2*a*, persistence of sensory effects after excision of ganglia, L⁵-S¹, inclusive. 3*a*, *b*, absence of sensory effects after excision of ganglion L⁴. Contralateral plexus, same animal; 4*a*, *b*, presence of sensory effects with stimulation of main pathways of this ovarian plexus. 5*a*, *b*, absence of sensory effects after excision of ganglion L³ alone. See text for discussion.

the fallopian tube, on the other hand, produced typical reflex responses on blood pressure and respiration (Fig. 1, 2, *a*, *b*).

We conclude from this series of experiments that the sensory fibers of the ovarian plexus issue from the ovary and tube and intimately follow the course of the ovarian vessels. When the ovarian vessels are severed, stimulation of the distal cut end produces no reflex response, but stimulation of the central end immediately causes a rise in the blood pressure and an increase in the rate and depth of respiration (Fig. 1, 7a, to 8b).

II. *Central Sensory Pathways of the Ovarian Plexus.*—These were determined by stimulation peripherally about the ovarian vessels after systematically destroying the sympathetic trunk at various levels. Fig. 2 illustrates the effect on reflex activity after removal of successive sympathetic ganglia beginning at the first sacral ganglion and proceeding upward through the lumbar chain.

These observations show that not until the fourth lumbar sympathetic ganglion is removed are the sensory responses from the ovarian plexus affected or abolished. Thus the sensory components of the ovarian plexus enter the main sympathetic trunk above the level of the fifth lumbar ganglion (Fig. 2, 3, a, b).

To prove that the animal was still responsive to stimulation and that the loss of reflex effects was not attributable to the progressive ganglionectomies from S¹ to L⁴, a shielded electrode was placed on the contralateral ovarian vessels. Stimulation of this intact ovarian plexus evoked an immediate reflex elevation in blood pressure and an increase in respiratory movements (Fig. 2, 4, a, b). Accordingly, the lowest essential sympathetic ganglion which receives sensory fibers from the ovarian plexus is L⁴. When the third lumbar ganglion on this side was removed, however, the remainder of the trunk, above and below including L⁴ being intact, the vascular and respiratory reflex effects were absent (Fig. 2, 5, a, b). This shows that the sensory fibers enter the fourth lumbar ganglion and pass upward through the third lumbar sympathetic ganglion to reach higher levels. This is true because if the fibers were to enter the fourth lumbar ganglion and then pass through the rami communicantes to enter the spinal cord at that level, transection of the third lumbar ganglion should not abolish the reflex responses.

Fig. 3 illustrates a series of experiments to show that the sensory fibers do not enter the spinal cord below the level of the second lumbar ganglion by way of the rami communicantes. Successive removal of the rami up to and including those at the level of the third lumbar ganglion failed to abolish reflex activity. However, transection of the main sympathetic trunk above the third lumbar ganglion then immediately caused cessation of reflex changes in blood pressure and respiratory movements (Fig. 3, 1a to 6b).

This group of experiments proves that the sensory fibers from the ovarian plexus travel along the ovarian vessels and enter the fourth

lumbar sympathetic ganglion. These fibers then run upward through the main sympathetic trunk beyond the third lumbar ganglion without passing to the spinal cord through the rami communicantes at these levels.

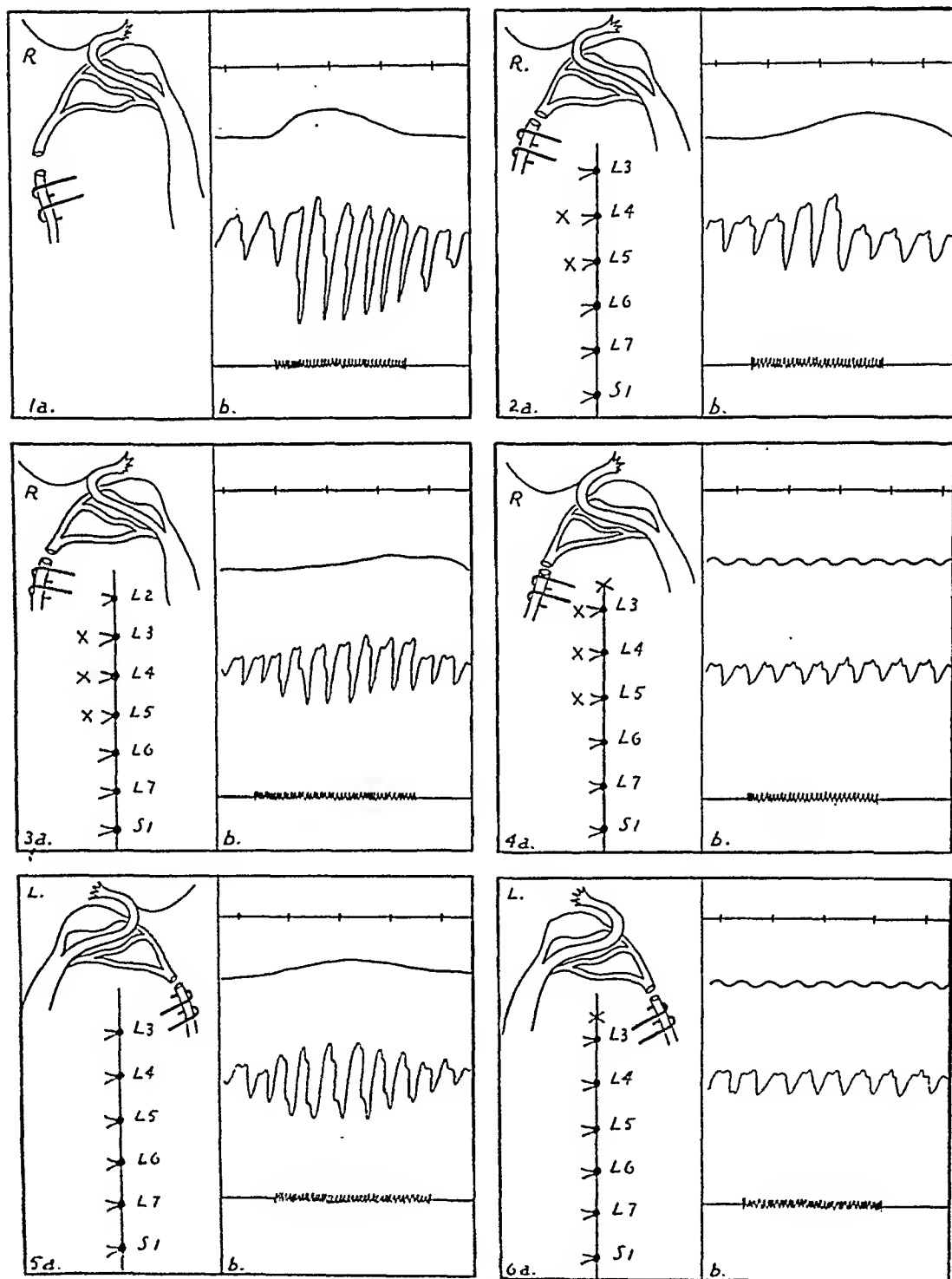


Fig. 3.—Figures showing that sensory fibers of ovarian plexus pass in the ganglionated chain to levels above L^2 . 1a, b, sensory effects of stimulating main pathway of ovarian plexus; 2a, b, and 3a, b, persistence of sensory effects after ablation of rami communicantes of L^2 , L^3 , L^4 inclusive; 4a, b, absence of sensory effects following section of ganglionated chain above L^2 . Contralateral plexus, same animal; 5a, b, usual sensory effects from stimulation of main pathways of ovarian plexus; 6a, b, absence of sensory effects after section of ganglionated chain between L^2 and L^3 , with all ganglia and rami communicantes intact. See text for discussion.

III. *Nonessentiality of the Superior Hypogastric Plexus.*—The sensory fibers from the uterus probably travel by way of the superior hypogastric plexus [Kuntz (1934) and preliminary observations of our own]. It should be a matter of interest and of some practical importance to determine whether or not the sensory fibers from the ovaries and tubes also pass through the superior hypogastric plexus, in view of the advocacy on the part of some investigators [Fontaine and Herrmann (1932), Elaut (1932), A. A. Davis (1934), Leriche (1927), Adson (1936), and others] for hypogastric nerve resection for pelvic pain.

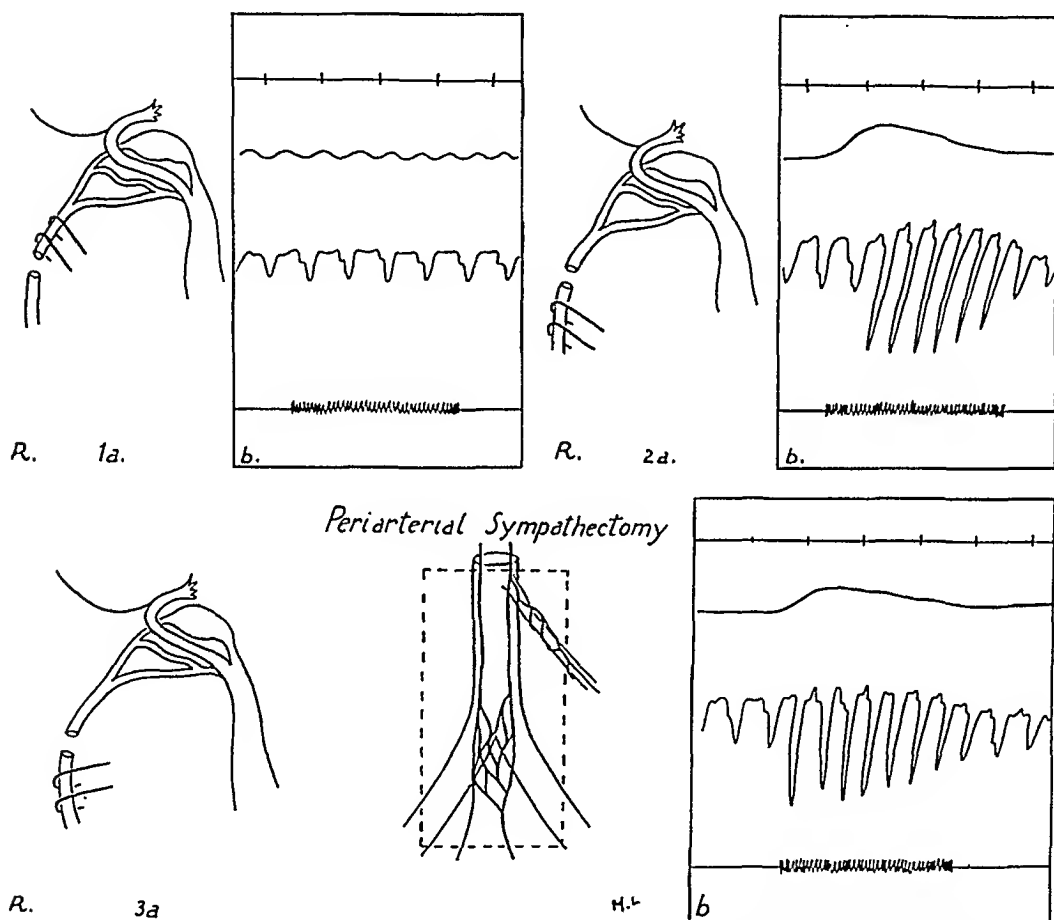


Fig. 4.—Figures showing the absence of sensory components of the ovarian plexus in the hypogastric plexus. 1a, b, absence of sensory effects upon stimulation of peripheral end of cut ovarian plexus, when all tissues from this point downward, to uterus, mesometrium and hypogastric plexus are intact. 2a, b, usual sensory effects upon stimulation of central end of cut ovarian plexus; 3a, b, persistence of sensory effects after complete periarterial sympathectomy. Ablation of ganglion L⁴ alone subsequently abolished the sensory effects. See text for discussion.

Fig. 3 illustrates a group of experiments which show that sensory fibers from the ovarian plexus do not go by way of the superior hypogastric plexus. In the first place stimulation of the peripheral cut end of the ovarian plexus does not produce any reflex responses on blood pressure and respiratory movements (Fig. 4, 1, a, b), even though the tissues are intact from the cut ovarian artery downward. Conceivably, if the afferent fibers pass downward within the broad ligament

to merge with the afferent components of the uterine plexus, stimulation of the peripheral cut end of the ovarian plexus should cause reflex rises in the blood pressure and respiratory movements. This is not the case, however.

To demonstrate this point still further, a shielded electrode was placed on the central end of the cut ovarian vessels. Then the lower portion of the abdominal aorta, the inferior mesenteric artery, the common iliac arteries, and the interiliac zone were completely denuded

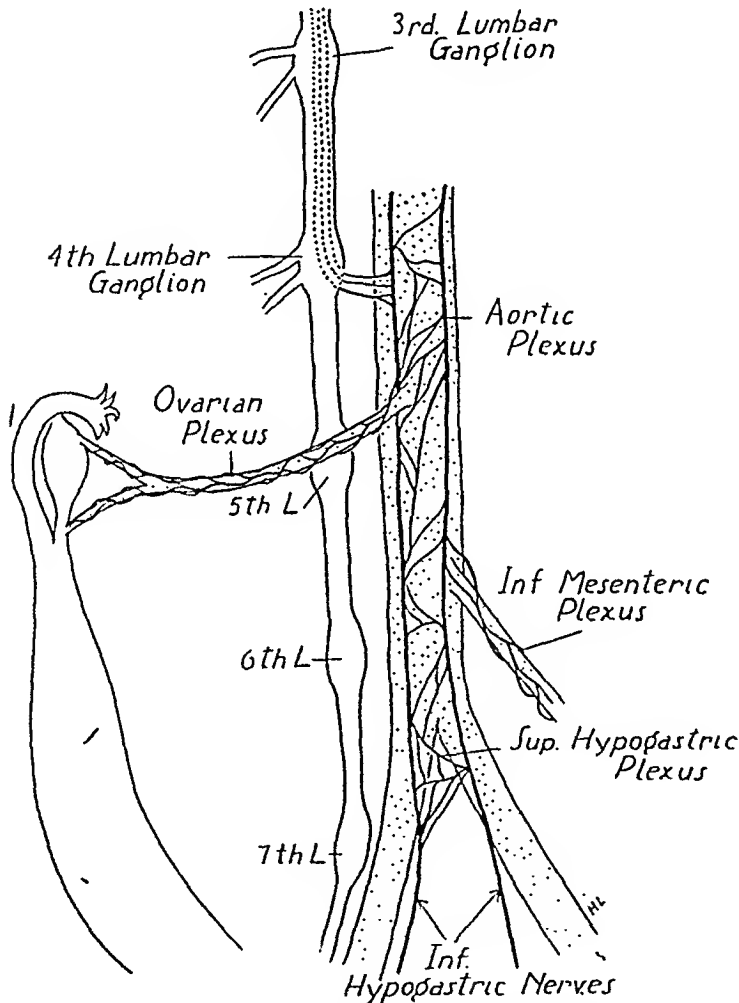


Fig. 5.—Schematic representation of the origin, course and distribution of the sensory components of the ovarian plexus. The sensory fibers enter the ganglionated chain at L⁴, pass through L⁵ to L⁶. None enter the spinal cord below L⁶, and none pass centrally through the inferior or superior hypogastric plexus.

leaving the entire sympathetic trunk intact. After such complete periarterial sympathectomy, faradic stimulation was applied through the shielded electrode. This immediately elicited a marked rise in blood pressure and respiratory movements (Fig. 4, 3, a, b).

These observations force us to the conclusion, therefore, that sensory fibers from the ovarian plexus do not pass through the superior hypogastric plexus but reach the central nervous system solely by follow-

ing the course of the ovarian vessels and entering the fourth lumbar sympathetic ganglion from which point they ascend to reach higher levels. It may be mentioned that, by the same token, they do not pass through the inferior mesenteric plexus or the lower portion of the aortic plexus.

DISCUSSION

That the afferent fibers from the ovary course along the ovarian artery has been suspected for some time. Kuntz (1934) states that the afferent components from the ovary travel along the ovarian plexus to reach the cord at the level of the tenth thoracic segment. Those of the fallopian tube course through the superior hypogastric plexus

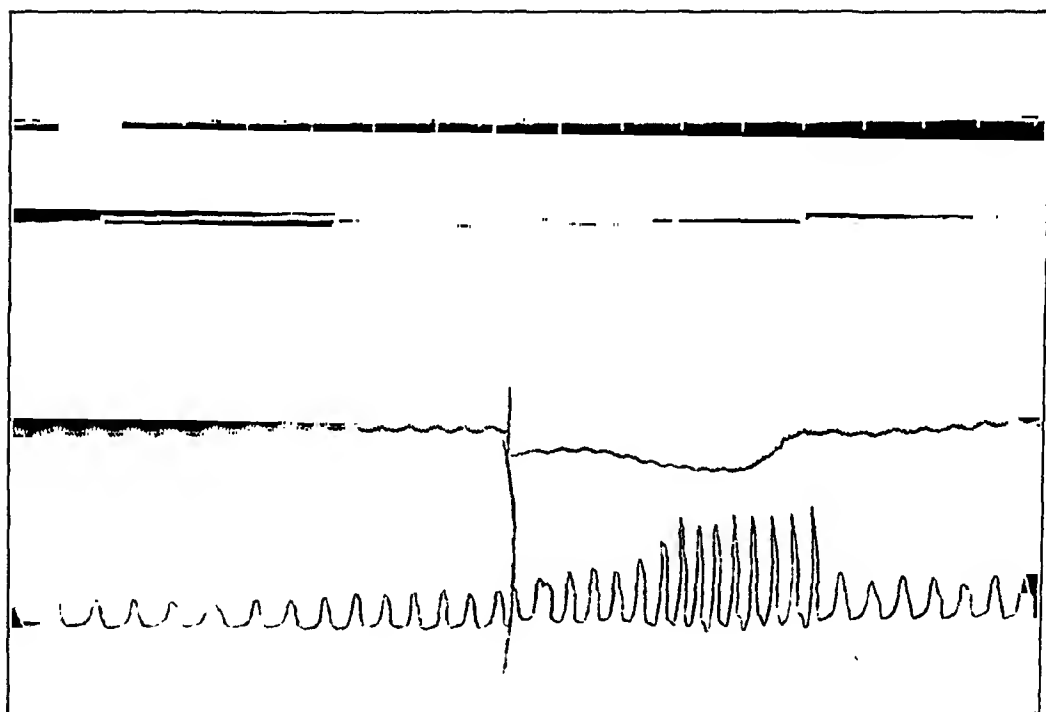


Fig. 6.—Kymographic recording showing increase in depth of respirations and elevation of blood pressure upon stimulation of the intact ovarian plexus. The record on the right shows the absence of such reflex effects after section of the ovarian plexus. The drawings for Figs. 1 to 3 were made from similar recordings.

to reach the cord at the level of the first lumbar to eleventh thoracic segments. Langley and Anderson (1895) considered the fibers of the ovarian plexus as relays from the inferior mesenteric ganglia. Dahl (1916) stated that the nerves to the ovary form a definite plexus arrangement following the course of the ovarian vessels.

However, we are not aware of any substantiating evidence in the literature pointing to the level that the ovarian afferents enter the main sympathetic trunk. The present group of experiments show that the sensory fibers run in close approximation to the ovarian vessels and enter the main sympathetic trunk through the fourth lumbar

ganglion. The afferents then travel upward through the main sympathetic trunk to enter the spinal cord at some level above the third lumbar ganglion (Fig. 5).

We have been unable to show the point of entrance of these sensory fibers into the spinal cord because of technical difficulties involved in tracing the fibers through the diaphragm and into the chest without affecting the sensory responses. To determine this it will be necessary to conduct chronic experiments in which the ganglionated chain is first cut at suitable points in the chest in a preliminary operation which is followed by acute experiments of the type reported in the present study.

CONCLUSIONS

1. A method has been described by which the course and distribution of the sensory components of the pelvic sympathetic nerves may be studied.

2. Applied to the ovarian plexus this study shows that:

- a. The sensory fibers originate in close relationship to the various peripheral branches of the ovarian artery.

- b. The afferents follow closely the course of the ovarian artery.

- c. They enter the fourth lumbar sympathetic ganglion and then traverse upward through the third lumbar ganglion to reach a higher level in the main sympathetic trunk.

- d. The ovarian afferent components have no connections by way of the superior hypogastric plexus, nor do they, by the same token, traverse the inferior mesenteric ganglia or the lower aortic plexus.

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Wirth, L.: *Nevus Telangiectaticus and Pregnancy*, *Monatschr. f. Geburtsh. u. Gynäk.* 102: 298, 1936.

The author reports a case of nevus telangiectaticus which did not appear until the third month of the first pregnancy. It became increasingly more conspicuous and disappeared after the puerperium. It returned, however, in a second pregnancy and disappeared again soon after the baby was born. The author does not believe that the nevus arose during the first pregnancy but that it was present in a latent form and became manifest for the first time during pregnancy.

J. P. GREENHILL.

ECLAMPSIA AND ITS SEQUELAE

A CLINICAL AND FOLLOW-UP STUDY OF ALL CASES AT BOSTON LYING-IN HOSPITAL OVER A TWENTY-YEAR PERIOD

HAROLD M. TEEL, M.D., AND DUNCAN E. REID, M.D., BOSTON, MASS.

(From the Department of Obstetrics, Harvard Medical School)

INVESTIGATION of the cardiovascular and renal sequelae of pregnancy toxemias, ideally should include only cases in which three factors are known.

First, the past histories of the patients studied, as these concern hypertensive disease and nephritis, should be definitely known. This is obvious since the common subsequent findings are hypertension and albuminuria.

Second, the family histories for hypertensive disease should be known. It is possible that patients destined to become hypertensives are more susceptible to pregnancy toxemias, including eclampsia, whether or not they have clinical hypertension at the time. Indeed, the stocky, florid patient who seems to be peculiarly susceptible to eclampsia is of essentially the same body type as the common hypertensive irrespective of pregnancy.

The importance of latent as well as of demonstrable hypertensive disease as contributory and complicating factors in many pregnancy toxemias has been pointed out by Corwin and Herriek¹ who stated, "That childbearing can reveal essential hypertension, when that disorder is latent, and aggravate it when it is actively present, is a fact that should be recognized by every obstetrician and every internist." However, even in their meticulous clinical and follow-up study of toxemic patients, prepregnancy data on blood pressure and urine were lacking in most cases.

Third, the duration and severity of the toxemia as indicated by the duration and severity of the hypertension and albuminuria should be known. On the basis of the established vasospastic mechanism of pre-eclampsia and eclampsia as presented by Irving,² it is reasonable to infer that prolonged and severe spasm, as indicated by marked hypertension and heavy albuminuria of considerable duration, should produce more permanent structural damage than transient or mild toxemia. Eclampsia shows the most marked vasospasm of the acute toxemias of pregnancy, and in this sense should result in more vascular damage than pre-eclampsia. However, the preceding toxemia, in cases of eclampsia, is not infrequently of brief duration. Whether a brief severe pre-eclampsia culminating in convulsions produces as much permanent vascular

damage as a prolonged noneonvulsive toxemia with marked hypertension and heavy albuminuria for many weeks would seem to be doubtful.

Such information as there is from follow-up studies would tend to indicate that subsequent vascular and renal damage is correlated more closely with the duration of the toxemia than with the maximum severity which may be reached momentarily during the course of the disease. Thus, Sym³ found that the longer the course of the "albuminuria" of pregnancy, the more likely the patient is to sequelae. He also found that one-fourth of the pregnancies which followed eclampsia were complicated by toxemia, whereas one-half of those following "albuminuria" of pregnancy were so involved.

Study of the vascular pathology in fatal cases of preeclampsia and eclampsia, as seen for example in the liver, kidney, adrenal, and spleen, gives clear indication of the marked narrowing of the arterioles, leading to ischemia, hemorrhage, and not infrequently to thrombosis. In such an organ as the kidney, thrombosis of the afferent glomerular arteriole would inevitably lead to destruction of the glomerular and tubular unit involved. Similarly, prolonged ischemia, as a result of arteriolar spasm, might conceivably lead to permanent damage of the functional unit supplied. This should be particularly true of organs supplied by the terminal type of circulation.

Among the cases of toxemia and eclampsia which occur in obstetric clinics, it is difficult to secure a significant number for follow-up study in which all three of the above-mentioned desiderata are available. In most instances, eclampsia results from ignorance and neglect on the part of the patient or her medical attendant. Consequently, patients who are treated in the obstetric clinics are usually first observed after convulsions have occurred, when the patient is in no condition to give an accurate medical history. Detailed histories taken subsequent to recovery reveal that a large proportion of these patients can give no positive information concerning the blood pressure and urine findings prior to or early in the involved pregnancy. Some have medical records of known hypertensive disease or nephritis, and a few more have records from insurance examination within a year or two of the eclamptic episode. In most cases, however, there is no reliable information as regards the blood pressure and urine findings prior to the eclamptic pregnancy. For this reason, it is often impossible, particularly in cases of eclampsia, to determine with certainty whether it has been superimposed upon preexisting vascular or renal disease. This is a very sad state of affairs, both from the practical and academic standpoint. Undoubtedly the immediate prognosis of eclampsia is altered considerably by preceding hypertension and nephritis. Furthermore, the incidence of hypertension or albuminuria which follows eclampsia cannot properly be related to it unless past medical histories are known.

The impression is common that eclampsia is rare in pregnant hypertensives and nephritics. We believe that eclampsia is infrequent in *known* hypertensives and nephritics because they are carefully watched and appropriately treated. For the same reason, eclampsia is rare in previously normal patients who develop preeclampsia under competent observation. It is our opinion that eclampsia is much more frequent among neglected hypertensives and nephritics than among neglected patients previously normal. Our autopsy material from fatal cases supports this opinion. Careful study of the pathology of 38 fatal cases of eclampsia by Acosta-Sison⁴ revealed evidence of chronic nephritis in 38.4 per cent. She included as nephritics, patients with both primarily parenchymatous and interstitial (vascular) kidney lesions.

We have made a study of all the eclamptic patients treated at the Boston Lying-In Hospital during the twenty-year period from 1915 through 1934. All patients included in the group had at least one convulsion. Only two fatal cases in which convulsions occurred have been excluded. One of these patients had a brain tumor, verified at autopsy, and the other had a brain abscess, also verified at autopsy. On the other hand, a number of nonfatal convulsive cases have been excluded because the convulsions were atypical, the blood pressure and urine findings were minimal, and past or subsequent histories reveal grand mal.

Statistical data for the whole group are briefly presented. In addition, for purposes of analysis and follow-up study, the patients have been divided into three groups with respect to their histories prior to the eclampsia. *Group I* includes only those patients without history of glomerular nephritis, whom we know from our own records to have had normal urine and blood pressure on more than one occasion during pregnancy prior to the eclampsia. *Group II* is made up of those patients who are known to have had hypertensive disease or chronic nephritis prior to the eclamptic pregnancy. *Group III* consists of those patients whose past histories as regards hypertension and nephritis are unknown. These patients were all admitted as emergencies, after the occurrence of convulsions, without records of blood pressure or urine prior to or during the involved pregnancy.

The patients have all been grouped upon objective evidence available at the time of the eclampsia. Excepting several instances in which the vascular system or kidneys at autopsy showed conclusive evidence of chronic disease independent of the eclampsia, we have not changed patients from the originally unknown into the known positive group; neither have we changed patients from the originally unknown into the known negative past history group on the basis of normal blood pressure and normal renal function tests subsequent to the eclampsia. This latter procedure, in one sense, would be justifiable, but it would make

an apparent decrease in the real incidence of hypertension and nephritis in the patients who were known to have been normal prior to the eclampsia.

This grouping of the patients is of some interest in relation to the immediate prognosis of the eclampsia, but it is vital in evaluating the cause and effect relationship between the eclampsia and subsequent cardiovascular and renal disease.

INCIDENCE

During the twenty-year period studied, eclampsia was treated 173 times in 168 patients. There were five instances of recurrent eclampsia. During the same period 55,426 patients were delivered in the hospital and out-patient services. The gross incidence of eclampsia was once for each 320 deliveries. However, 127 of the eclamptic patients were transferred to the clinic as emergencies by private physicians, and other hospitals, after convulsions had occurred. Of the patients who were registered in the clinic and who had made one or more visits, 46 developed eclampsia. Thus, the incidence of eclampsia among patients under care of the clinic was approximately one in 1,200 deliveries. Many of the clinic patients in whom eclampsia developed had failed to meet appointments or refused hospital admission earlier in pregnancy. Indeed, the more carefully cases of so-called "fulminating eclampsia" are studied, the less frequent such cases appear to be. It thus appears that with reasonable cooperation of the patient during the prenatal period, careful check of weight gain, edema, urine, blood pressure, and symptoms, combined with timely treatment and interference, would make it possible, practically, to eliminate eclampsia.

The seasonal incidence of our cases is not remarkable. There were 38 cases from January through March, 49 cases from April through June, 47 cases from July through September, and 39 cases from October through December. Thus, the incidence was slightly greater during the warm season.

MORTALITY—INFLUENCE OF SOURCE OF PATIENT, TYPE OF ECLAMPSIA, AGE, AND PARITY

The mortality figures are offered with no corrections. In the deaths are included patients who died within a few minutes after admission as well as several patients who died of sepsis, weeks after delivery. Total deaths among the 173 cases were 46 (26.6 per cent). Of the fatal cases, 39 occurred among the 127 emergency cases (30.7 per cent), and of the 46 clinic cases, seven died (15.2 per cent). Thus, the emergency patients, who contributed 73.4 per cent of the eclampsia, accounted for 85 per cent of the fatalities. We suspect that the high death rate among the emergency patients may be explained in large part by two circumstances. First, many of these patients were moved over considerable

distances after the occurrence of convulsions. A number of them were transferred from their homes first to another hospital and then to this clinic. Second, the incidence of eclampsia superimposed upon preexisting hypertension and nephritis was much higher in the emergency group. Among the clinic cases with hypertension and nephritis, eclampsia was largely prevented by a combination of frequent observations, medical regime, and termination of the pregnancy upon indication.

The eclampsia was severe according to the classification of Eden in 118, or 68.2 per cent of the patients. Of the severe cases, 43 died (36.4 per cent). Of the 55 mild cases, three ended fatally (5.5 per cent).

In 101 cases the convulsions began antepartum. Fatalities in this group were 34 (33.6 per cent). Three of the 25 patients with intrapartum eclampsia died (12 per cent), and among 45 postpartum cases there were nine deaths (20 per cent).

There were 96 patients less than thirty years of age of whom 18 died (18.7 per cent). Of the remaining 77 patients over thirty years, 28 ended fatally (36.3 per cent).

Primiparas and multiparas were about equal in number, there being 85 of the former with 18 deaths (21.2 per cent) and 88 of the latter with 28 deaths (31.8 per cent). The higher mortality among the multiparas and older patients might reasonably be correlated with the greater incidence of preceding hypertensive disease and nephritis in these groups.

Division of the cases into three groups according to their histories as regards hypertensive disease and nephritis preceding the eclampsia results in marked differences in the mortality rates. The groups are made up as previously described.

Group I: (Negative past history.) There were 39 patients in this group with four deaths (10.3 per cent).

Group II: (Positive past history.) Of the 13 known hypertensives and nephritic patients who developed eclampsia, eight died (61.5 per cent).

Group III: (Unknown past history.) Of the 121 patients in this group, 34 died (28.1 per cent).

As might be anticipated, the mortality was highest in the small group with preceding hypertensive disease or nephritis, intermediate in the patients with unknown past history and lowest in the group with eclampsia known to have been uncomplicated by preceding vascular or renal disease.

TREATMENT

Significant discussion of these cases as regards method of treatment and mortality rate is impossible because the series goes back to the time when immediate accouchement forcé, bagging, and cesarean section were in vogue. The number of patients treated by modern and more conservative methods is too small to be of significance. Suffice it to state

that of 24 patients delivered by immediate abdominal or vaginal hysterotomy, 12 died (50 per cent). It would be hazardous to attribute all these deaths to the cesarean section per se. Doubtless, ill-advised choice of anesthesia and coincident medical treatment played important contributory rôles.

COMPLICATIONS IN FATAL CASES

Of the 46 fatal cases, death was preceded by acute pulmonary edema in 26, uremia in 4, shock and hemorrhage in 3, and cerebral hemorrhage in 2. In five instances the patient "faded out" without ascertainable cause. The following complications were observed in single instances, severe diabetes, lobar pneumonia, pneumonia with "hepatic insufficiency," sepsis with empyema, and sepsis with rheumatic heart disease.

The relatively high incidence of acute pulmonary edema in the fatal cases (56 per cent) is of interest.* It suggests that the immediate cause of death in eclampsia is frequently left ventricular failure. This opinion is supported by the occasional occurrence of severe cardiac asthma with acute pulmonary edema in cases of severe preeclampsia with or without preceding vascular, cardiac, or renal disease (Teel, Reid and Hertig⁵).

FETAL MORTALITY

Records are available on 171 of the babies of these patients. The gross fetal mortality was 51 per cent. The eclampsia occurred before the thirty-fourth week of gestation in 27.2 per cent of the cases, which accounts in part for the high fetal mortality. The fates of the babies are summarized with respect to birth weights in Table I.

TABLE I. FETAL MORTALITY IN 171 BABIES OF ECLAMPTIC MOTHERS

WEIGHT	LIVED	NEONATAL DEATHS	STILLBIRTHS	TOTAL
Under 5 pounds	27	14	40	81
5 to 6 pounds	13	5	12	30
Over 6 pounds	44	2	14	60
Total	84	21	66	171

FOLLOW-UP STUDY

We have made every effort to learn the subsequent fate of each patient who survived eclampsia. In locating the patients, inquiries have been made of relatives, friends, and family physicians. City directories, police lists, and voting lists have been used. The Community Health Nursing Association has located several patients, and a number have been traced through the In- and Out-Patient Departments of the large community hospitals. Finally, the name of each patient who has not

*We have included only those patients with signs of acute pulmonary edema for several hours before death. We believe that we have not confused it with agonal rhonchi.

been located has been sought among the death certificates for the state of Massachusetts for each year subsequent to our last record.

There have been eight deaths among the 127 patients who survived eclampsia:

M. D. was readmitted to this hospital as an eclamptic emergency at the age of twenty-two, three years after her first eclampsia, with recurrent antepartum eclampsia complicated by severe abruptio placentae. She died of uremia with suppression of urine, seven days postpartum. At the time of the first eclampsia the past history had been unknown. Autopsy was refused.

R. L. was readmitted to this hospital as an eclamptic emergency at the age of thirty-nine, eight years after the first seizure of eclampsia. She died four days postpartum of recurrent antepartum eclampsia. The autopsy revealed lobar pneumonia and rheumatic heart disease with mitral stenosis and mitral vegetations. The kidneys were of normal size, and the capsule stripped readily, leaving a few small surface scars. The cortices were essentially normal, and the kidneys were otherwise not remarkable.

A. M. was admitted to another hospital at the age of forty, eighteen months after her eclampsia at this clinic. She was suffering from another severe toxemia of pregnancy (possibly eclampsia) from which she died. No autopsy was performed.

K. O. was admitted to another hospital thirteen months after her eclampsia, at the age of forty-six. On admission she was in coma with a complete right hemiplegia and signs of congestive failure. The blood pressure was 200 systolic, 140 diastolic, but the catheter urine showed no albumin. She died four days after admission, and the clinical diagnosis was hypertension with cerebral hemorrhage. This patient had been treated for hypertension before the eclamptic pregnancy. No autopsy was performed.

H. C. was admitted to a psychiatric institution at the age of forty-five, eighteen years after her eclampsia, with complaints of stupor, unresponsiveness, facial palsy, and incontinence of urine. There was a history of hypertension for more than a year, with milder but similar cerebral symptoms. The blood pressure was 230 systolic, 130 diastolic, and the heart was enlarged. The urine concentrated to 1.031 and showed no albumin. The diagnosis was cerebral arteriosclerosis and hypertension. The patient gradually failed and died. No autopsy was performed. There was no record of the blood pressure of this patient prior to her eclampsia.

G. K. died at home at the age of forty-one, five years after her eclampsia. The diagnosis of the attending physician was lobar pneumonia and chronic nephritis. The blood pressure and urine findings were unknown prior to the eclamptic pregnancy, but nine months after delivery there was moderate elevation of the blood pressure, and the urine contained a slight trace of albumin in a voided specimen. She probably had hypertension at the time of her death, and may have been a nephritic.

M. C. died at home at the age of forty-nine, seven years after her eclampsia. The diagnosis of the attending physician was mitral stenosis with cardiac decompensation. There was no autopsy, and the patient may well have died of hypertensive heart disease. At least, there was no evidence of mitral stenosis at the time of her eclampsia. Whether this patient had hypertension or albuminuria prior to the eclampsia is also unknown.

F. S. died at the age of thirty-nine, five years after her eclampsia, from carcinoma of the cervix. There was no hypertension at the time of her death.

Thus, of the eight patients who have died subsequent to their recoveries from eclampsia, three succumbed to recurrent pregnancy toxemias, of which two were recurrent eclampsia. Of the remaining five,

three are known to have had hypertensive disease and one may have had nephritis. None of the hypertensive deaths occurred in patients whose histories were known to be negative and whose blood pressures and urine were known to have been normal prior to the eclampsia.

At present, the remaining 119 survivors of eclampsia are presumably alive. We have failed to communicate with 32 of them, although none has died in any of the larger community hospitals, and death certificates have not been filed for any of them in the state of Massachusetts, subsequent to our last record. In seven instances we have corresponded with patients whom we were unable to examine.

The remaining 80 patients have all been examined, one or more times, at intervals of from more than one year to twenty-one years. The average interval between the eclampsia and the last examination is 7.6 years. Blood pressure readings and urine examinations have been secured upon all patients. In more than 50 of them complete physical examinations with seven-foot heart plate, electrocardiogram, and urea clearance test have been made. The cardiology of these patients will be reported elsewhere.

SUBSEQUENT HYPERTENSION AND ALBUMINURIA

Because of the fact that nearly all of the clinic patients who developed eclampsia were known to have had blood pressures below 140 systolic and urine free of albumin earlier in pregnancy, and since we believe that this was not the case with a considerable proportion of the emergency patients, we have separated them in the follow-up study. Notwithstanding the small groups, the separation seems to be justified.

Of the 80 patients examined, the blood pressure was above 150 in 22 (27.5 per cent). There were 31 clinic patients in the group, of whom only three had systolic pressures over 150 (9.7 per cent). In each of the three instances the hypertension was disclosed at examination more than 15

TABLE II. BLOOD PRESSURE AT FOLLOW-UP EXAMINATION IN 80 PATIENTS FROM ONE TO TWENTY-ONE YEARS FOLLOWING ECLAMPSIA

Average interval after the eclampsia is 7.6 years. The patients are arranged in two groups depending upon whether they attended the prenatal clinic or were admitted as emergencies.

YEARS F. U.	1-4 YR.		5-9 YR.		10 YR.		TOTAL		GRAND TOTAL
SYSTOLIC BLOOD PRESSURE	EMERGENCY	CLINIC	EMERGENCY	CLINIC	EMERGENCY	CLINIC	EMERGENCY	CLINIC	
Less than 140	6	7	8	7	9	7	23	21	44
140-149	3	4	0	3	4	0	7	7	14
150-174	1	0	1	0	6	1	8	1	9
175-199	1	0	1	0	1	0	3	0	3
200.	3	0	3	0	2	2	8	2	10
Total	14	11	13	10	22	10	49	31	80

years after the eclampsia, without interval follow-up, so that it is impossible to determine when the hypertension developed with relation to the eclampsia. Of the 49 emergency patients examined at follow-up, 19 (38.8 per cent) showed systolic pressures over 150. The data on the subsequent blood pressures are summarized in Table II.

Only seven of the 80 patients showed albuminuria at follow-up examination (8.7 per cent). None of the patients who had attended the clinic showed albuminuria at examination more than one year postpartum.

The 80 followed patients fell into the three above-defined groups with reference to history of hypertension or nephritis prior to the eclamptic pregnancy as follows:

Group I: (Known normal before eclamptic pregnancy.) In this group there were 29 who were followed. The systolic pressure was above 150 in three of them (10.3 per cent). These three patients were all more than fifteen years postpartum.

There were no instances of albuminuria in this group.

Group II: (Known hypertensives or nephritics before eclamptic pregnancy.) There were only four patients in this group. All of them had systolic pressures above 175.

Group III: (Unknown histories for hypertension or nephritis prior to the eclamptic pregnancy.) There were 47 patients in this group of whom 15 had systolic pressures above 150 (31.9 per cent). All of the seven instances in which albuminuria was found were in this group.

The data for the blood pressure values in the patients grouped upon past history for hypertension or nephritis at the time of the eclampsia are summarized in Table III.

TABLE III. FOLLOW-UP BLOOD PRESSURES* FROM ONE TO TWENTY-ONE YEARS IN 80 PATIENTS WHO SURVIVED ECLAMPSIA

The patients are arranged in three groups on the basis of positive, negative, or unknown history for hypertension or nephritis at the time of the eclampsia.

SYSTOLIC BLOOD PRESSURE	KNOWN NORMAL			UNKNOWN HISTORY			KNOWN NEPHRITIC OR HYPERTENSIVE			TOTAL			GRAND TOTAL
	1-4 YR.	5-9 YR.	10+ YR.	1-4 YR.	5-9 YR.	10+ YR.	1-4 YR.	5-9 YR.	10+ YR.	1-4 YR.	5-9 YR.	10+ YR.	
To 139	6	7	7	7	8	9	0	0	0	13	15	16	44
140-149	4	2	0	3	1	4	0	0	0	7	3	4	14
150-174	0	0	1	1	1	6	0	0	0	1	1	7	9
175-199	0	0	0	0	0	1	1	1	0	1	1	1	3
200-	0	0	2	3	1	2	0	2	0	3	3	4	10
Total	10	9	10	14	11	22	1	3	0	25	23	32	80

*The average follow-up period is 7.6 years.

UREA CLEARANCE TEST

In 50 patients the urea clearance test was done at follow-up examination. The results are shown in Table IV.

It will be seen that of 23 patients known to have been free of hypertension and nephritis prior to the eclampsia, the urea clearance test

showed values above 60 per cent in all cases. The single urea clearance below 50 per cent (28 per cent clearance) was obtained from a patient with known hypertension prior to the eclamptic pregnancy. There is record of impaired renal function with marked hypertension and nitrogen retention in one patient who was treated subsequent to her eclampsia at another hospital. The past history of the patient was unknown at the time of the eclampsia, and we have been unable to follow her.

TABLE IV. THE UREA CLEARANCE TEST IN FOLLOW-UP STUDY OF 50 ECLAMPTICS

All tests were performed at intervals of from more than one to twenty-one years after the eclampsia. Average interval was six years.

UREA CLEARANCE VALUE (PER CENT)	UNDER 50	50-59	60-69	70-79	80-89	90-99	100+	TOTAL PA- TIENTS
Group I*	-	-	1	5	2	5	10	23
Group II*	1	-	-	-	1	-	-	2
Group III*	-	2	3	5	5	1	9	25
Total	1	2	4	10	8	6	19	50

*The patients are arranged in groups according to their past histories at the time of the eclampsia, as previously described.

Group I. Known negative past history for hypertension and nephritis.

Group II. Known to have had hypertension or nephritis, prior to the eclampsia.

Group III. History as regards hypertension and nephritis prior to the eclampsia is unknown.

The results of the urea clearance tests in this series of patients suggest that if "chronic nephritis" is a frequent sequel of eclampsia, it seldom progresses to the point of renal insufficiency.

SUBSEQUENT PREGNANCIES

There have been 100 pregnancies in 48 of the followed patients.

Some degree of hypertension or albuminuria was shown in 31 of them. There were five instances of recurrent eclampsia.

Of 45 pregnancies which occurred in 20 patients who were known to have been free of hypertension and nephritis before the eclamptic pregnancy, 17 were complicated at some time during the pregnancy by systolic blood pressure of 140 or more, or albuminuria, or both. There was one instance of recurrent eclampsia in this group. It is interesting that this patient, who had eclampsia twice, subsequently had a baby without signs of toxemia. Of the 45 babies, 40 survived. One of the five fetal deaths was not associated with toxemia.

The more recent follow-up studies of eclamptic patients bring out two definite points. First, the incidence of hypertension in patients who have had eclampsia is significantly greater than in patients following normal pregnancy. Breakey⁶ in an interesting study showed clearly that the incidence of hypertension was higher in a series of 132 women who had had eclampsia from one to twenty-one years before than in 218

control patients from the same clinic who were delivered without toxemia. The incidence of hypertension was greater in the eclamptic group irrespective of age. On the basis of systolic blood pressure of 140 or more, the incidence of hypertension was 42.5 per cent in the eclamptic group and 33.72 per cent in the controls. On the basis of 150 systolic, the figures were 26.5 per cent and 21.6 per cent, respectively. The studies of Corwin and Herriek,¹ Herriek and Tillman,⁷ Nevermann,⁸ Schultz,⁹ Sym,³ Peekham¹⁰ and others show similar results. Second, chronic nephritis subsequent to eclampsia, in the sense of chronic glomerulonephritis, pyelonephritis, and significantly impaired renal function, is uncommon. To be sure, the incidence of subsequent "chronic nephritis" has been estimated as 25 per cent and more. Unfortunately, in many of the earlier studies "chronic nephritis" was confused with hypertension. Of definite chronic nephritis on the basis of clinical study and renal function tests, the incidence is not great. Nevermann found three cases among 60 studied eclamptics. Greenhill¹¹ found five cases in the follow-up study of 60 eclamptic patients. However, four of them had been known to have had nephritis prior to the eclampsia. Sym reports two cases of chronic nephritis among 74 post-eclamptic patients. It should be pointed out that in none of these studies is it positively stated whether all of the eclamptic patients followed were known to have been free of hypertension and nephritis before the eclampsia.

It is of interest that in our cases, both the immediate eclamptic mortality and the incidence of subsequent hypertension and albuminuria have been materially lower among patients who had attended the prenatal clinic prior to the eclampsia than among those who were admitted as emergencies. There are probably a number of reasons why this should be true.

As regards the immediate mortality, it would seem that at least three factors have been operative in explaining the lower death rate among the clinic patients. *First*, the latter received more prompt hospitalization, with a minimum of transportation and confusion, after convulsions occurred. *Second*, among the clinic patients the course of the hypertension and albuminuria prior to the eclampsia was relatively brief. On the other hand, the duration of the toxemia preceding convulsions was frequently prolonged in the emergency patients. A number were known, by their physicians, to have had marked hypertension and albuminuria for many weeks before the onset of convulsions. It would seem that prolonged exposure of the system to the injurious effects of severe toxemia, before the onset of convulsions, might well make such patients poorer risks. *Third*, and most important, among the clinic patients the eclampsia was rarely superimposed upon preexisting hypertension or nephritis. Eclampsia in the emergency patients was often complicated

by preexisting hypertension, and less commonly, by nephritis. There can be little doubt that hypertensive and nephritic patients who develop eclampsia do poorly. Objectively, they constitute the majority of the "severe" cases, according to the classification of Eden.

The mortality rates of these patients when divided into groups on the basis of reliable past history for hypertension and nephritis, prior to the eclampsia, tend to bear out the above contention. Thus, the mortality rate among the patients known to have been free of hypertension and nephritis, before the eclampsia, was 10.3 per cent. Of the known hypertensive and nephritic patients, who developed eclampsia, it was 61.5 per cent. The mortality in the remaining group, in which the past history was unknown, was intermediate (28.1 per cent).

In the follow-up study of these patients two observations deserve emphasis. First, by far the most common abnormal subsequent finding is hypertension (27.5 per cent). Albuminuria is much less frequent (8.75 per cent). The answer to the question whether this hypertension is primarily vascular or renal in origin is suggested by the renal function tests. Of 50 cases in which the urea clearance test was done, only one was definitely abnormal. This clearance was obtained from a patient known to have had hypertension prior to the eclampsia. She showed no clinical evidence of significantly impaired renal function, and unfortunately the test could not be repeated. Concentration tests and examination of the urine sediment in many cases failed to reveal evidence of significantly impaired renal function. Second, such symptoms as were found in patients at follow-up examination were largely referable to hypertensive disease, i.e., dyspnea, orthopnea, vertigo, paroxysmal dyspnea, and headache.

Although in this series of cases, subsequent hypertension has been frequent (27.5 per cent), one may not unqualifiedly infer from this that eclampsia results in hypertensive disease in so great a proportion of the cases. In a significant proportion, the hypertension was present before the eclamptic pregnancy; in others it may have been latent, and in others still, it may have developed subsequent to and independent of the eclampsia. The incidence of hypertension among parous women of comparable age who had not had toxemia was found to be 21.6 per cent (Breakey). Of our 29 followed patients who were known to have been free of hypertension and nephritis prior to the eclampsia, only three subsequently showed systolic pressures over 150, and these three patients were all more than fifteen years postpartum at the time of the last examination.

It would be difficult to believe that prolonged and severe toxemia, in previously normal patients, should not leave some irreparable vascular damage. That this is true is suggested by the high incidence of some degree of toxemia in later pregnancies even though the blood pressure

and urine are normal in the nonpregnant state. Undoubtedly the low incidence of subsequent hypertension (9.7 per cent) and the absence of albuminuria in our clinic cases is to be correlated with the circumstance that in them previous hypertensive disease, and nephritis were absent and the eclampsia was not preceded by prolonged and severe preeclampsia. Among the emergency patients, the greater incidence of subsequent hypertension (39.8 per cent) may have been due in part to the more prolonged course of the preceding toxemia which frequently occurred.

SUMMARY

A study has been presented of 173 patients with eclampsia who were treated at the Boston Lying-In Hospital during the twenty-year period from 1915 through 1934. The uncorrected mortality was 26.6 per cent. The mortality for patients who had attended the clinic prior to the development of eclampsia was less than for those admitted as emergencies. The mortality was higher in multiparas than in primiparas and was also higher in patients over thirty years of age. Reasons for these differences are discussed.

Of the 127 survivors of eclampsia, eight have subsequently died; three of recurrent pregnancy toxemias, two of severe hypertension with cerebral lesions, one of cardiac decompensation, probably of vascular origin, one of lobar pneumonia complicated by hypertension and possibly chronic nephritis, and one of cancer of the cervix. Eighty of the patients who survived the eclampsia have been followed from more than one to twenty-one years. The average follow-up interval is 7.6 years. The incidence of hypertension among these patients was 27.5 per cent, and the incidence of albuminuria 8.75 per cent. Evidence of significantly impaired renal function was found in only one case.

The patients were studied in groups with reference to their past histories as these concerned hypertensive disease and nephritis prior to the eclampsia. A significant number of them had hypertensive disease or nephritis prior to the eclampsia, and both the immediate and remote outlook for these patients was considerably poorer than for those known to have been normal before the eclampsia. Of the 29 patients followed who were known to have been healthy prior to the eclampsia, the incidence of subsequent hypertension was 10.3 per cent and that of albuminuria was nil. Such symptoms as were encountered at follow-up examination were largely explicable on the basis of hypertensive disease.

CONCLUSIONS

1. Eclampsia is frequently complicated by preexisting hypertensive disease and less commonly by chronic nephritis.
2. The immediate mortality of uncomplicated eclampsia is much lower than when it is superimposed upon preexisting hypertensive disease of nephritis.

3. The most common abnormal finding at follow-up study in patients who have had eclampsia is hypertension. In this series of cases its incidence was 27.5 per cent. The incidence of albuminuria at follow-up study was 8.75 per cent. These figures do not represent the true incidence of these two findings as sequels to eclampsia, for hypertensive disease and, less commonly, nephritis were sometimes present before the eclamptic pregnancy. Of 29 postecclamptics followed who were known to have been healthy prior to the eclampsia, none had albuminuria or evidence of impaired renal function, and only three (10.3 per cent) showed hypertension.

4. Such damage as occurs as a result of eclampsia would appear to be primarily vascular in character. Chronic parenchymatous nephritis, and significantly impaired renal function are uncommon sequelae.

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Banssillon, E., and Mounier-Kuh, P.: Concerning One Form of Epistaxis During Pregnancy. Bleeding Polyps of the Septum, Bull. Soc. d'obst. et de gynéc. 25: 71, 1936.

Ordinarily nasal bleeding during pregnancy is not common and is not serious. The cause is usually ascribed to congestion due to pituitary action. In most cases examination reveals a simple congestive hypertrophy. Some authorities consider hemorrhages from the nose as symptoms of toxemias of pregnancy. The authors report an unusual case of nasal bleeding from a large polyp in the septum. This polyp disappeared spontaneously.

J. P. GREENHILL.

Pillay, A. P.: Birth Control in India: Necessity and Methods, J. Indian M. A. 5: 732, 1936.

The necessity for birth control in India is great. The author discusses the question of contraception as a public health measure and describes methods suitable for the poor to adopt. The well-to-do can afford diverse care.

The medicated tampon and a rubber sponge are means available for the poor. The tampon or sponge is soaked in a solution of equal parts of lemon juice and water or any bland oil. A reliable jelly may be prescribed.

Vaginal sterilization of the mother or vasectomy in the man are methods sometimes indicated.

F. L. ADAIR AND S. A. PEARL

THE MECHANISM OF THE PROLONGATION OF PREGNANCY IN THE RABBIT*

ARTHUR K. KOFF, M.D., AND M. EDWARD DAVIS, M.D., CHICAGO, ILL.

(From the Department of Obstetrics and Gynecology, the University of Chicago and the Chicago Lying-In Hospital)

THE length of gestation varies considerably in the different mammals and in the same species. Thus the rat carries her young an average of 20 days, the rabbit 30 to 32 days, the monkey 178 days, the chimpanzee 251 days, and the human female 267 days. Variations in the same species have been carefully studied by Hartman in the maeaque monkey, in which animal it has been possible to make accurate observations. He noted a variation in the length of pregnancies in different animals but a less marked variation in the several pregnancies in the same animal.

Usually labor sets in spontaneously at term, so that normally the mature fetus is rarely retained in the uterus beyond this time. Like all biologic phenomena, there are exceptions in which labor fails to take place at the proper time, resulting in prolongation of gestation. While this is a rare occurrence, dire effects may result for the mother and her offspring because of the excessive size of the latter and the abnormal labor mechanism in the former. The biologic mechanism, by which the fetus is retained in the uterus until complete development and the initiation of labor at its termination, must be delicately balanced. The explanation of this mechanism has received considerable attention but as yet it has not been elucidated.

Of the many theories that have been advanced as an explanation of the normal mechanism for the termination of pregnancy, only two are worthy of serious consideration in the light of present-day scientific knowledge. One, the greater irritability of the uterus associated with an increase in the frequency and intensity of the intermittent contractions, finally eventuates in labor. In support of this theory, there is the increasing susceptibility of the uterus to mechanical stimulation and oxytocics as term is approached. The second is the hormonal theory, which presupposes the elaboration of a hormone by the corpus luteum which desensitizes the uterus to the action of the posterior pituitary gland. As term approaches this hormonal influence decreases, lowering the receptive threshold to hormonal and oxytocic stimuli.

In the light of our present work, a combination of the two theories may reflect the truth. More and more evidence is accumulating which suggests that the retention of the fetus in the uterus until maturity and the mechanism by which labor is initiated are both under hormonal control. Experimental studies of normal gestation, its artificial pro-

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longation and termination in the rabbit, offer an excellent approach to the problem. Undoubtedly, there are great species differences but the fundamental principles underlying the process may be the same in all mammals.

The physiology of reproduction in the rabbit is such that the process lends itself to experimental work in this field. It is for this reason that many fundamental processes have been worked out with the aid of this animal and a great deal of knowledge has been accumulated. Normally, the mature rabbit does not ovulate until ten hours after copulation. The absence of spontaneous ovulation and the regularity with which it occurs following mating are well-known biologic phenomena. Fertilization frequently results from a single copulation, thus further simplifying the exact determination of the onset of gestation. Hammond and Marshall have concluded that the average duration of gestation in the rabbit is thirty-two days, a fact which has been amply corroborated.

The development of a normal decidua in the uterus, the proper implantation of the growing embryos and the continuation of their normal development are all dependent on the maintenance of the corpora lutea. Ancel and Bouin demonstrated that the removal of the corpora lutea by castration or their destruction results in a failure of the mucous membrane to develop the typical progestational phase necessary for implantation. Furthermore, the embryos develop for several days but fail to implant on reaching the uterine horns. Weymeersch and others have established the fact that the removal of the ovaries in the second half of gestation in rabbits is invariably followed by abortion or premature labor. This observation has been amply confirmed by many workers in this field.

It can thus be concluded that in the rabbit the exact time of onset of gestation is known and under control. Furthermore, the proper development of the pregnancy and its successful continuation to term are directly controlled by the maintenance of the corpora lutea.

More recently, Corner, Allen and their coworkers have isolated a hormone from the corpus luteum, progesterin, which can be successfully substituted for the normal corpora lutea in the rabbit. Their experiments prove that the development of a normal decidua in the uterine horns, the implantation of the embryos in the uterus and their successful growth and delivery at term can be accomplished in the absence of ovaries and their corpora lutea by the substitution of extracts of corpora lutea given daily by intramuscular injections. These interesting observations add another link in the chain of evidence that the corpus luteum controls gestation in the rabbit.

Asehheim and Zondek, Snyder and Wislocki, Hill and Parkes have all noted the fact that human pregnancy urine contains a substance which causes ovulation in pregnant rabbits. The new corpora lutea thus produced resemble the natural ones in every way, although according to Hill and Parkes their life is somewhat shorter and they produce more rapid involution in the corpora lutea already present. Although ovulation has been induced in animals other than the rabbit, the ease with which this can be accomplished depends largely on the dose and route of administration of the human pregnancy urine.

Snyder found that a single dose of 40 rat units per kilo of an extract of pregnancy urine (antuitrin-S) given intravenously would induce ovulation and develop a new set of corpora lutea in the pregnant rabbit. Furthermore, when this was carried out on the twenty-fifth day of normal gestation, the pregnancy failed to terminate at term but continued on for approximately fifteen days after injection, the life span of the new corpora lutea. It can be seen that new corpora lutea produced on the twenty-fifth day reach their maximum development and function about the thirty-second day, thereby disturbing the normal hormonal mechanism for the termination of pregnancy.

Watts, in 1935, reported that impure preparations of growth hormone of the anterior lobe of the pituitary produced a prolongation of pregnancy in rats of two to five days, as well as an alteration in the birth mechanism.

We repeated the experiments of Snyder, using a series of 15 pregnant rabbits. Animals that had been isolated were mated once and again isolated. Following the successful copulation, pregnancy was confirmed by careful palpation and, when necessary, by x-ray. Under these carefully controlled conditions thirty to sixty rat units of pregnancy urine extract (Parke, Davis and Company, antuitrin-S) were injected intravenously on the twenty-fifth day of the gestation. Abortions occurred in five of the animals on the twenty-sixth to the twenty-eighth day. These aborted fetuses were all living, normal in appearance, but definitely premature. In three of these cases the abortions probably took place as a result of too large a dose of the anterior pituitary-like substance. The mechanism of abortion is not entirely clear. However, the stimulation of follicular maturity by the pregnancy urine extract may result in a marked increase in the estrin content. It has been shown by Parkes and Bellerby that large doses of estrin will cause the early interruption of pregnancy in animals (Table I).

The ten rabbits that received 40 rat units per kilogram of body weight failed to go into labor at term. The pregnancy was prolonged from five to ten days, terminating spontaneously or artificially by cesarean section. When the pregnancy was prolonged beyond the thirty-sixth day, the fetuses were invariably dead at delivery. Those born alive were considerably larger than normal and more fully developed, indicating their postmaturity. The fetuses that were dead showed the usual signs of maceration and early absorption so typical of retained dead fetuses.

The birth mechanism sets in sometime between the thirty-eighth and forty-third day. This additional period probably represented the life span of the corpora lutea. With the waning influence of these new corpora, the retarded mechanism for the onset of gestation could now assert itself. As Snyder pointed out, the labors were likely to be prolonged, difficult and abnormal, partly due to the increased sizes of the fetuses because of overdevelopment. In several of the animals, one or two living fetuses were delivered twenty-four to seventy-two hours following the injection of the pregnancy urine extract, but the remaining fetuses in the litter would remain in the uterus, continue to develop

TABLE I. THE DURATION OF PREGNANCY FOLLOWING INTRAVENOUS INJECTION OF HUMAN PREGNANCY URINE EXTRACT*

NO. OF RABBIT	PARITY	DAYS PREG-NANT AT INJEC-TION	A.P.L. SUBSTANCE (ANT.-S) GIVEN INTRA- VENEUSLY	DURATION OF PREGNANCY (NORMAL 30-32 DAYS)	CHARACTER OF DELIVERY	FINDINGS AT AUTOPSY OR LAPAROTOMY	FATE OF FETUSES
87	2	25	40 units/kg.	35	Cesarean	6-7 fresh corpora lutea	7 living postnaturo
88	2+	25	40 units/kg.	34-35	Spontaneous—prolonged labor	4 fresh corpora lutea; necrosis of uterine wall	1 living on 34th day; 7 dead on 35th day; no maceration
102	1+	24	40 units/kg.	37	Spontaneous	None	3 dead, macerated
104	1	25	40 units/kg.	34	Spont.—72 hr. +	None	8 living postnaturo
119	1	25	30 units/kg.	41	Spont. 1, C.S. 4	8-15 new corpora; necrosis of uterine wall	4 macerated
131	1+	25	40 units/kg.	36	Spont.	None	8 macerated
134	1+	25	40 units/kg.	43	Abortion, 1 fetus on 27th day. Lap. on 26th day, 1 ovary removed	Fresh corpora. Normal uterine wall	1 living 8 macerated
136	1+	25	40 units/kg.	38	Spont., 8 fetuses on 43rd day. Abortion 27th day. 1 dead, young. 38 days: 3 postmaturo—dead	None	4 dead, macerated
140	1+	25	40 units/kg.	34	Cesarean	8-12 fresh corpora	6 living 6 dead, early maceration
170	2+	25	40 units/kg.	37	Spont. (prolonged)	None	3 living
118	1	25	40 units/kg.	26	Abortion—spont.	8-15 fresh corpora	6 living
133	1	25	60 units/kg.	27	Abortion—spont.	None	9 living
135	1	25	50 units/kg.	27	Abortion—spont.	None	3 living, 2 dead
141	3	25	60 units/kg.	27	Abortion 27th and 28th days. Lap., left ovary removed 24th day. Abortion: spont. 28th day. Right ovary removed 28th day	8 fresh corpora	6 living
169	1	25	40 units/kg.	28			

*Antuitrin-S, Parke, Davis & Company.

until the thirty-sixth or thirty-seventh day, succumb and finally be delivered as macerated fetuses at about forty days. This again is evidence of a disturbed birth mechanism (Fig. 4).

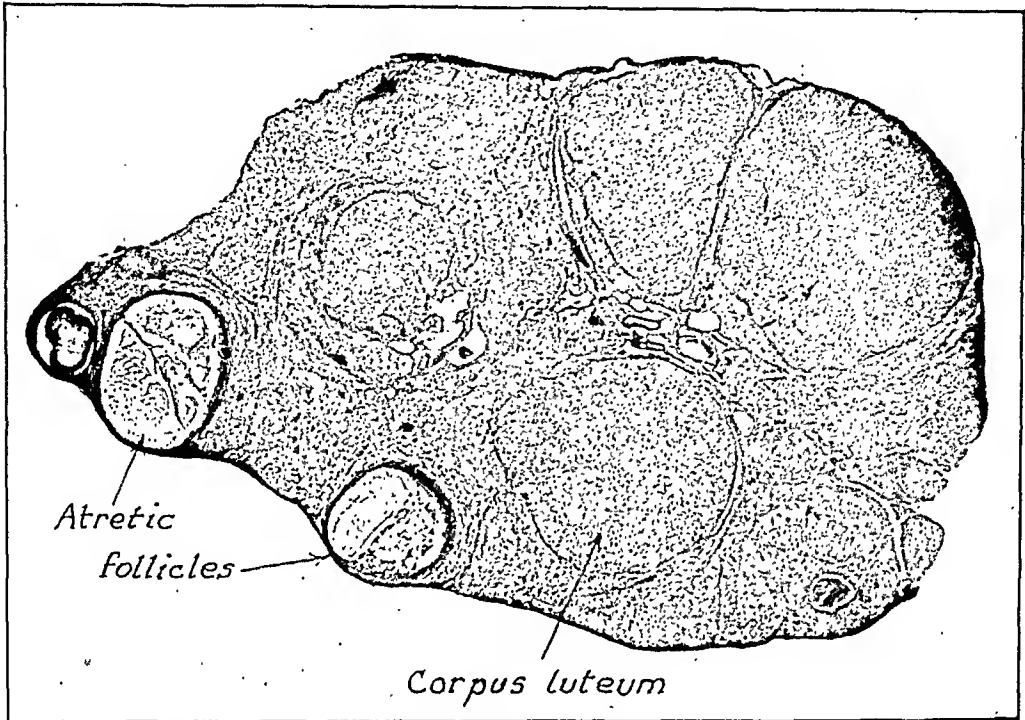


Fig. 1.—Left ovary (Rabbit 169) removed on twenty-fourth day of gestation prior to injection of antuitrin-S, showing well-developed corpora lutea and atretic follicles, corresponding to twenty-fourth day of normal gestation. (X16)

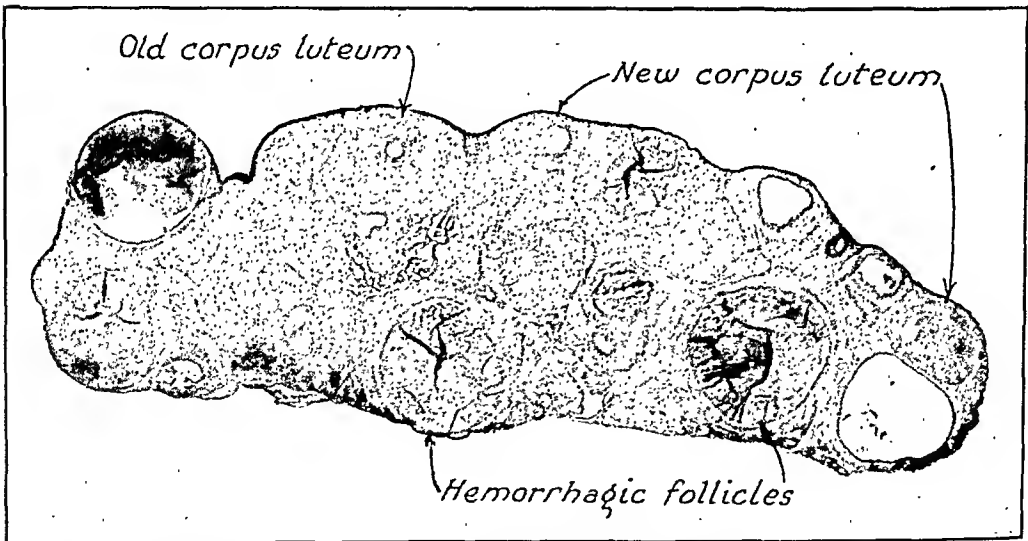


Fig. 2.—Right ovary (Rabbit 169) removed on twenty-eighth day of gestation three days following injection of 40 units per kilo of antuitrin-S, showing numerous old and newly developed corpora lutea and hemorrhagic follicles induced by antuitrin-S. (X8)

Laparotomy before the death of the fetuses usually revealed normal uterine horns distended with large, post-term fetuses. On removing

them from the uterus respiration would be initiated promptly. The ovaries were irregularly nodular and two distinct sets of corpora lutea could be seen. Histologic sections of these ovaries show these two sets of corpora distinctly. One group is retrogressing while the second group shows all the evidences of full maturity (Figs. 1, 2, and 3).

Laparotomy after the thirty-sixth day of gestation revealed dead fetuses in the uterine horns in various stages of maceration and early absorption. Their postmortem characteristics were well defined, indicating their prolonged intrauterine existence. In the ovaries the artificial set of corpora lutea likewise showed evidences of retrogression but this process was much more manifest in the first set of follicles.

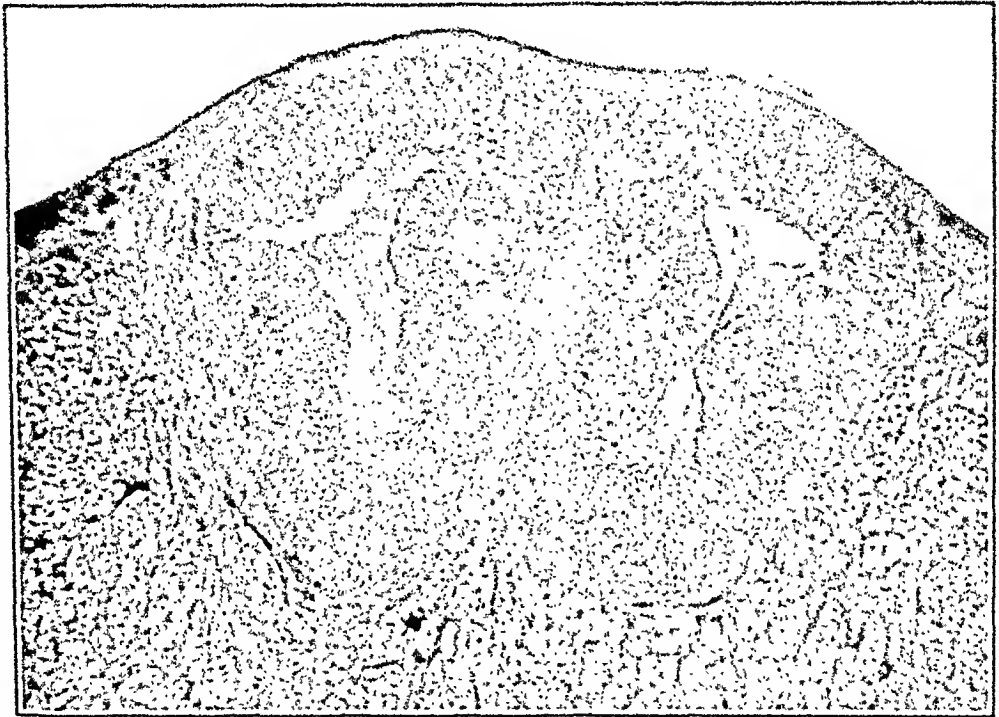


Fig. 3.—Right ovary (Rabbit 153), two newly developing corpora lutea following injection of 10 units per kilo of antlutrin-S. Note residual hemorrhage in the central cavity and tortuous margin of corpus luteum cells of collapsed follicle. (875)

In several of our animals, the hemorrhagic extravasation into the uterine musculature with signs of early necrosis was observed, as noted by Snyder. These changes in the uterus probably set in with the onset of labor. We are at a loss to explain their significance.

These carefully controlled experiments confirm the important rôle that the corpus luteum plays in the regulation of gestation and its proper termination. If new active corpora lutea, induced artificially, can inhibit the onset of labor at term, extracts of the corpus luteum injected into the animals should be able to do the same thing. The success of such experiments would definitely establish the fact that the hormone elaborated by the corpus luteum itself was the direct or indirect etiologic agent involved in the artificial prolongation of gestation.

TABLE II. THE DURATION OF PREGNANCY FOLLOWING INTRAMUSCULAR INJECTION OF CORPUS LUTEUM EXTRACT

NO. OF RABBIT	DAILY INJECTIONS DURING GESTATION		DOSE	DURATION OF PREGNANCY (NORMAL 30-32 DAYS)	CHARACTER OF DELIVERY (LABOR)	AUTOPSY OR LAPAROTOMY	FATE OF FETUSES
	FROM DAY	THROUGH DAY					
151	25	33	2 R.U. (proluton)	27	Cesarean section	No new corpora	6 living
154	25	33	2 R.U. (proluton)	30	Prolonged 72 hr.		4 living
155	25	34	2 R.U. (proluton)	31	Prolonged		5 living
165	25	33	2 R.U. (proluton)	32	Prolonged		5 living
166	25	35	2 R.U. (proluton)	32	Prolonged		3 dead, 8 macerated
168	25	30	1 R.U. (proluton)	32	Normal	No fresh corpora	7 living
173	25	34	2 R.U. (C.L.P. Winthrop)	33	(Lap., left ovary removed)		8 postmature
174	25	31	2 R.U. (C.L.P. Winthrop)	33	Prolonged	No fresh corpora	3 living, 2 dead
175	25	32	2 R.U. (C.L.P. Winthrop)	34	Prolonged 48 hr.		7 living
177	24	26	2 R.U. (C.L.P. Winthrop)	34	Abortion, ovaries removed 28th day		5 living
178	25	32	2 R.U. (C.L.P. Winthrop)	36	Normal		5 living
179	25	32	2 R.U. (C.L.P. Winthrop)	36	Normal		6 living, 1 dead
130	25	38	2 R.U. (progesterone B.D.H.)	39	Prolonged	No new corpora	4 macerated
1A	27	36	5 Int. U. (progesterone*)	36	Cesarean	No fresh corpora, normal	7 large dead, early maceration
2A	28	37	5 Int. U. (progesterone)	38	Cesarean	No fresh corpora	6 large, early maceration
4A	28	33	5 Int. U. (progesterone)	36	Delivered 3 days following last dose of progesterone		5 large, macerated
5A	28	33	5 Int. U. (progesterone)	34	Cesarean	No new corpora	6 living
6A	28	41	5 Int. U. (progesterone)	41	Cesarean	No new corpora	7 dead, macerated
7A	28	40	5 Int. U. (progesterone)	42	Spontaneous		9 macerated

* (Proluton, Schering) 1 mg. crystalline progesterone = 1 international unit.

About this time, potent corpus luteum extraets became available and, most recently, crystalline progestin, progesterone, was introduced. The experiments with these potent preparations can be divided into two groups (see Table II and Fig. 4). In the first group, twelve pregnant rabbits were given daily intramuscular injections of two rabbit units of progestin in oil, beginning on the twenty-fifth day of the gestation and continuing until the termination of the pregnancy. These preparations were obtained from two different sources but both were accurately standardized. Of this group, gestation was prolonged to the thirty-sixth day in two animals and the thirty-fourth day in two others. The remaining rabbits delivered between the thirtieth and thirty-fourth day. In one

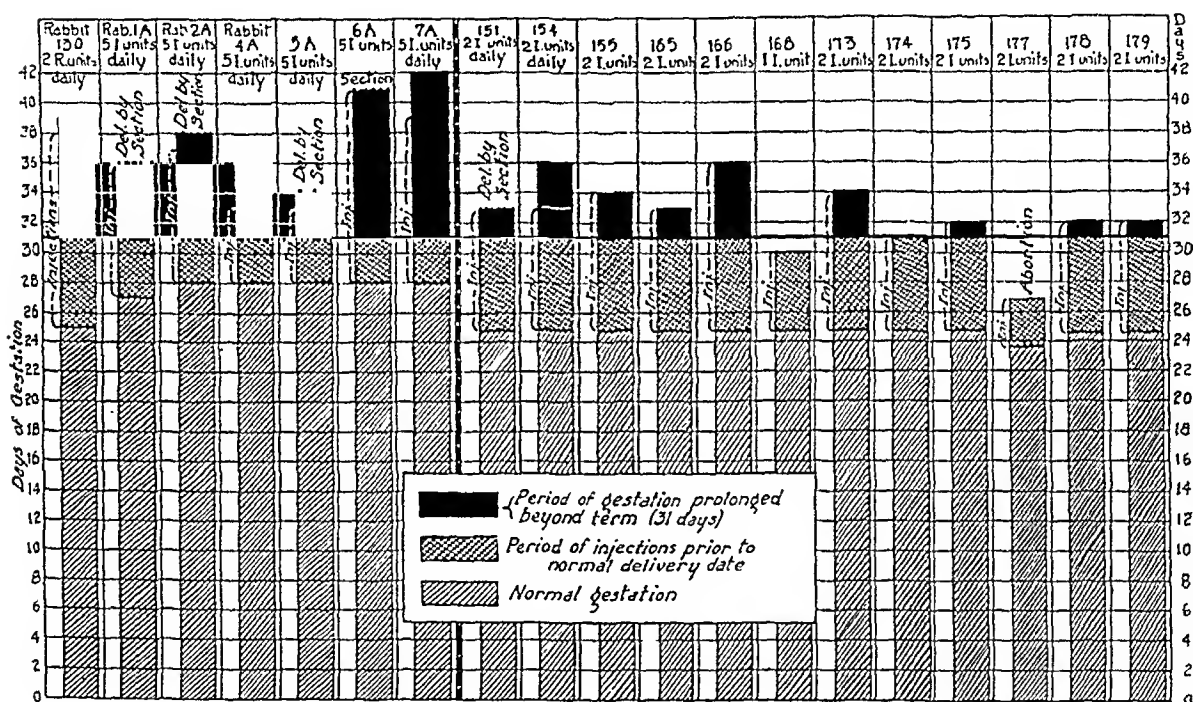


Fig. 4.—Graphic representation of Table II.

animal in which the pregnancy lasted thirty-six days, all the fetuses were delivered dead. Fetuses delivered between the thirty-third and thirty-sixth days showed evidences of postmaturity by their unusual size and state of development. Their mothers experienced prolonged and difficult labors.

The second group of animals received 5 mg. or 5 international units of crystalline progestin, progesterone, intramuscularly at daily intervals beginning on the twenty-eighth day of their gestations, and continued until the pregnancy was terminated either naturally or artificially. None of these animals went into labor at term but continued with their gestations until the hormone was discontinued, whereupon they went into labor twenty-four to forty-eight hours later. Sufficient experiments have not been carried out to determine whether the birth mechanism

can be permanently held in abeyance by the continued injection of progesterone until the fetuses have been extensively or completely absorbed. It is our impression, however, that this is possible. None of the rabbits went into premature labor during the administration of the hormone. It is likewise noteworthy that the fetuses succumbed about the thirty-sixth day and appeared in the same state of preservation following their death, as previously described. Those that survived were large, obviously postmature. When the birth mechanism was finally initiated, the labor was unduly prolonged, sometimes lasting forty-eight to seventy-two hours, in contrast with the normal length of two to four hours. This may be due to the excessive size of the offspring, but the



Fig. 5.—Ovary (Rabbit 7A) removed on forty-second day of gestation, ten days past term. Old corpus luteum showing marked involution, fibrosis and vacuolization of cells. ($\times 75$)

effect of progestin in diminishing the irritability or contractile power of the uterine muscle may also be factors.

Laparotomy performed on the thirty-sixth day or later revealed the uterus abnormally distended with living or dead fetuses. No hemorrhage or necrosis was evident in the uterine musculature. The ovaries were relatively smooth, pale, of normal size and showed no evidences of new follicle development or recent corpora lutea (Fig. 5).

These latter experiments add another link to the chain of evidence which definitely binds the corpus luteum to the rôle it plays in the control of the gestation. The hormone of the corpus luteum alone, in sufficient quantities, can inhibit the onset of labor and prolong the gestation. It is obvious from the foregoing experiments that a daily dose of

about 5 mg. of progesterone is necessary to inhibit the birth mechanism. Less than this amount may be ineffective as can be seen from Table II. It is possible that the minimum amount necessary was exceeded. Corner found that in a pregnant rabbit spayed at the eighteenth hour of the gestation, the use of corpus luteum extract will permit normal implantation and carry the fetuses to full term, providing the daily dose of the extract is at least five times that amount necessary to produce typical progestational changes. The rapidity of the hormonal action can be seen in that its use was delayed to the twenty-eighth day of the gestation.

DISCUSSION

A number of observations have been made by investigators in this field which throw some light on the mechanism by which pregnancy in the rabbit is prolonged. Reynolds and Knaus have noted the fact that corpus luteum extracts relax uterine muscle. Knaus found that in vitro preparations of rabbits' uteri, which are normally very sensitive to pituitrin, become refractory to the drug during the first half of pregnancy and during pseudopregnancy. In the latter part of pregnancy, however, the inhibiting effect of the corpus luteum diminishes and the muscle fibers become more sensitive to pituitary extract, so that the response of the uterus to pituitary extract when administered at term is immediate and powerful, and results in the volcanic onset of labor. In animals where pregnancy is being prolonged because of a new artificial set of corpora lutea or by the daily injections of progesterone, pituitary extract, even in large doses, has no effect in initiating labor. In experiments by Snyder and confirmed by us in rabbits under the influence of progesterone, pituitary extract in 1 c.c. doses given intravenously at term failed to cause uterine contractions. This inhibition of action of the drug persists until the corpus luteum effect has worn off. These experimental observations suggest that the mechanism by which gestation is prolonged resides in a diminished responsiveness of the uterine musculature to the usual stimuli that initiate labor. When the threshold of receptiveness has been lowered sufficiently by the removal of corpus luteum inhibition so that the uterine musculature is again responsive, labor sets in.

The corpus luteum in the human being does not seem to exert as fundamental a rôle as in the rabbit. Asdell found 34 cases recorded in the literature in which the corpus luteum was supposedly removed by castration during gestation between the first and seventh months, and all but four went to term without interruption. Obviously these cases do not represent the only occurrences of this kind, but they do emphasize the fact that in the human species the conditions necessary for the successful termination of gestation are not wholly dependent on the corpus luteum. It is possible that once decidual development takes place so

that normal implantation can occur, the rôle of the corpus luteum in the human female is taken over by some other tissue or organ like the placenta. Thus, van Lankeren found that a considerable amount of progesterin could be extracted from the human placenta at any time during pregnancy. More recently, Philipp demonstrated the presence of progesterin in the urine of the newborn which likewise may have been derived from the placenta.

Our initial experiments on this problem concerned themselves with crude extract of human corpora lutea removed during various periods of gestation. Daily injections of these extracts failed to produce the typical progestational phase in mature virgin rabbits. Daily implants of fresh corpora lutea likewise contained too little progesterin to influence the experimental animals. In one case, however, extracts prepared from two human corpora lutea removed in the first trimester produced a doubtful response. These experiments indicate that the human corpus luteum in the latter half of gestation is a poor source for progesterin.

The death of post-term fetuses, at approximately the same period in the gestation, is another interesting observation. Why these fetuses die when they have reached a certain age is difficult to explain. Progesterone is not toxic to mother or fetus and can be administered throughout gestation without untoward effects. Where fetuses were aborted following the administration of pregnancy urine extract they were alive and normal. Neither the lack of sufficient progesterin nor its oversupply influences the fate of the fetus other than its premature delivery in the former instance. It must be concluded that altered environmental conditions result in its postmature fate.

In the human female, intrauterine death of the postmature fetus has often been noted and recorded. Kaern found that there was a definite relationship between postmaturity, excessive size of the fetus, and intrauterine death. Of 228 newborn infants weighing 4500 gm. or over, 116 mothers had a calculated duration of pregnancy of 291 days or over. The fetal mortality in this entire group was 14.9 per cent. Nine of these children were dead and macerated at the onset of labor, an incidence of 4 per cent. This can be compared with a gross fetal mortality from all causes of 3.3 per cent in the same clinic. Does this result mean an insufficiency of the placenta because of retrogressive changes in its substance, resulting in a gradually diminishing blood supply to a fetus rapidly increasing in size? The underlying pathology may reside in the progressive changes in the placental site because of retrogressive vascular changes. It is not likely that the fetus is in itself responsible for its postmature intrauterine termination. It is undoubtedly the victim of uteroplacental changes, the result of an environment obviously not meant for continuing the intrauterine existence of the fetus much beyond its normal period.

CONCLUSIONS

The corpus luteum hormone, progesterin, is directly responsible for the maintenance of the pregnancy in the rabbit and its normal termination. The prolongation of gestation can be accomplished in two ways: First, by the induction of ovulation at the twenty-fifth day of pregnancy with the use of pregnancy urine extract. These new corpora lutea reach their maximum development and functional activity at term, thereby inhibiting the onset of labor and prolonging gestation until their influence has subsided, about fifteen days. Second, progesterone, crystalline progesterin, can be substituted for new corpora lutea when given in sufficient amount by daily intramuscular injections, beginning as late as the twenty-eighth day of the gestation. It will likewise inhibit the onset of normal labor at term and prolong pregnancy as long as the injections are maintained. Labor usually sets in twenty-four to forty-eight hours following the cessation of the administration of progesterone. The uterus is not responsive to huge doses of pituitary extract when under the influence of progesterin. It can thus be concluded that the maintenance of an adequate supply of corpus luteum hormone at term and beyond it definitely inhibits the onset of the birth mechanism.

When pregnancy is prolonged by new corpora lutea or by progesterone, large postmature fetuses are produced. If these are delivered before the thirty-sixth day of the gestation, they are alive and normal. Intrauterine death invariably occurs about this time, although the fetuses may be retained in the uterus as long as it is under corpus luteum influence. The cause of the intrauterine death of the fetuses when pregnancy is unduly prolonged is under investigation. These experimental findings have their analogy to many pathologic conditions in the human female.

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PRIMARY DYSMENORRHEA—AN ENDOCRINE PROBLEM*

JACOB KOTZ, M.D., F.A.C.S., AND

ELIZABETH PARKER, M.A., M.D., WASHINGTON, D. C.

(From the George Washington University School of Medicine, Department of Obstetrics and Gynecology)

DYSMENORRHEA offers one of the most difficult problems encountered in the practice of gynecology. In reviewing the literature one is impressed by the wide divergence of opinion which has existed in the past as to the incidence, the cause, and the treatment of dysmenorrhea. With such a multiplicity of views on the subject, one naturally questions whether the underlying nature of the disturbance has been uncovered. Certainly the results of therapy have been far from constant and satisfactory.

Recent advances in endocrinology have suggested that some endocrine imbalance might be the cause of menstrual pain. Our study is an attempt to discover if there is a disturbance in the endocrine mechanism of menstruation in patients suffering from dysmenorrhea which causes pain, and if so, its nature, cause, and possible treatment. We have approached the problem from two angles, namely, that of the laboratory and that of the clinic.

The laboratory approach consisted of assays of the blood and urine of patients suffering from dysmenorrhea for the estrogenic and gonadotropic substances. The Frank-Goldberger technique¹ was used in assaying the blood and urine for the estrogenic substance, the Aschheim-Zondek concentration technique for the gonadotropic substance in the urine and the Fluhman technique for the determination of the gonadotropic element in the blood. The 100 cases so studied fall into three groups:

Group I: This included fifteen unmarried women, ages sixteen to twenty-six, who complained of dysmenorrhea but who were otherwise normal. Blood studies were made once a week for one complete menstrual cycle and again the following month within five days of menstruation, for the purpose of titration. The results obtained are shown in the graphs shown in Fig. 1. Of the estrogenic substance only one patient had a level lower than normal. In twelve cases there was a demonstrable amount of the substance throughout the cycle, and rising to a peak just prior to the onset of menstruation at which time a mouse unit was found in 30, 20, and even in 10 c.c. of blood. In none of the cases was a positive Fluhman test obtained. In this group of

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eases of dysmenorrhea the findings were a higher than normal level of blood estrogenic substance and a normal or subnormal amount of the gonadotropic substance.

Group II: To determine whether or not the high blood level of the estrogenic substance found in Group I was due to excessive production or faulty elimination, a second group of 15 cases was studied in which the blood was assayed, as in Group I and at the same time the urine was titrated for the amount of estrogenic and gonadotropic substances excreted during one monthly cycle. The results are summarized in Fig. 2. Here again is found a high blood level of the estrogenic substance. The general character of the excretion curve follows that of normal, but there is an excessive amount of the estrogenic substance throughout

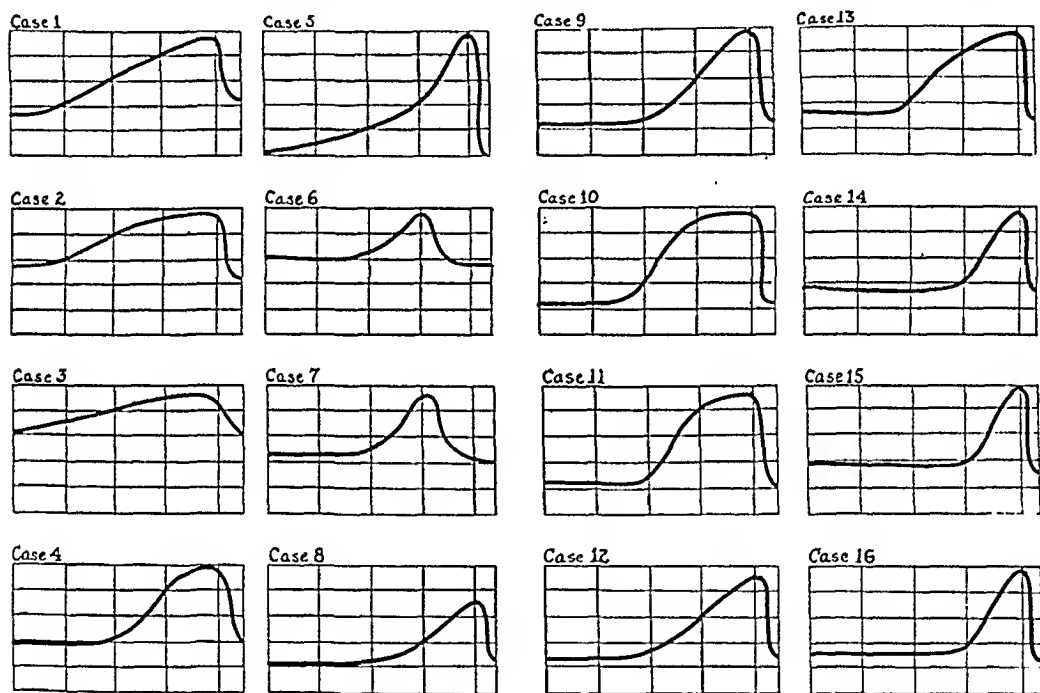


Fig. 1.

the cycle, the total amount being from two to four times that of normal. For the gonadotropic substance in the blood none of the patients gave a positive Fluhman test. Eight patients had a positive reaction in the urine, all occurring at about midperiod, a finding which is normal. Seven patients gave negative reactions throughout the cycle in the urine.

From these findings it seems safe to conclude that a high blood level of estrogenic substance is present in a large percentage of cases of functional dysmenorrhea, and that this is not due to faulty elimination by the kidneys, since the urine level is also higher than normal. Also, the gonadotropic factor in the blood and urine is either normal or less than normal in amount.

Group III: This comprises seventy unselected cases of dysmenorrhea in which no organic pathology was demonstrable, in which single blood

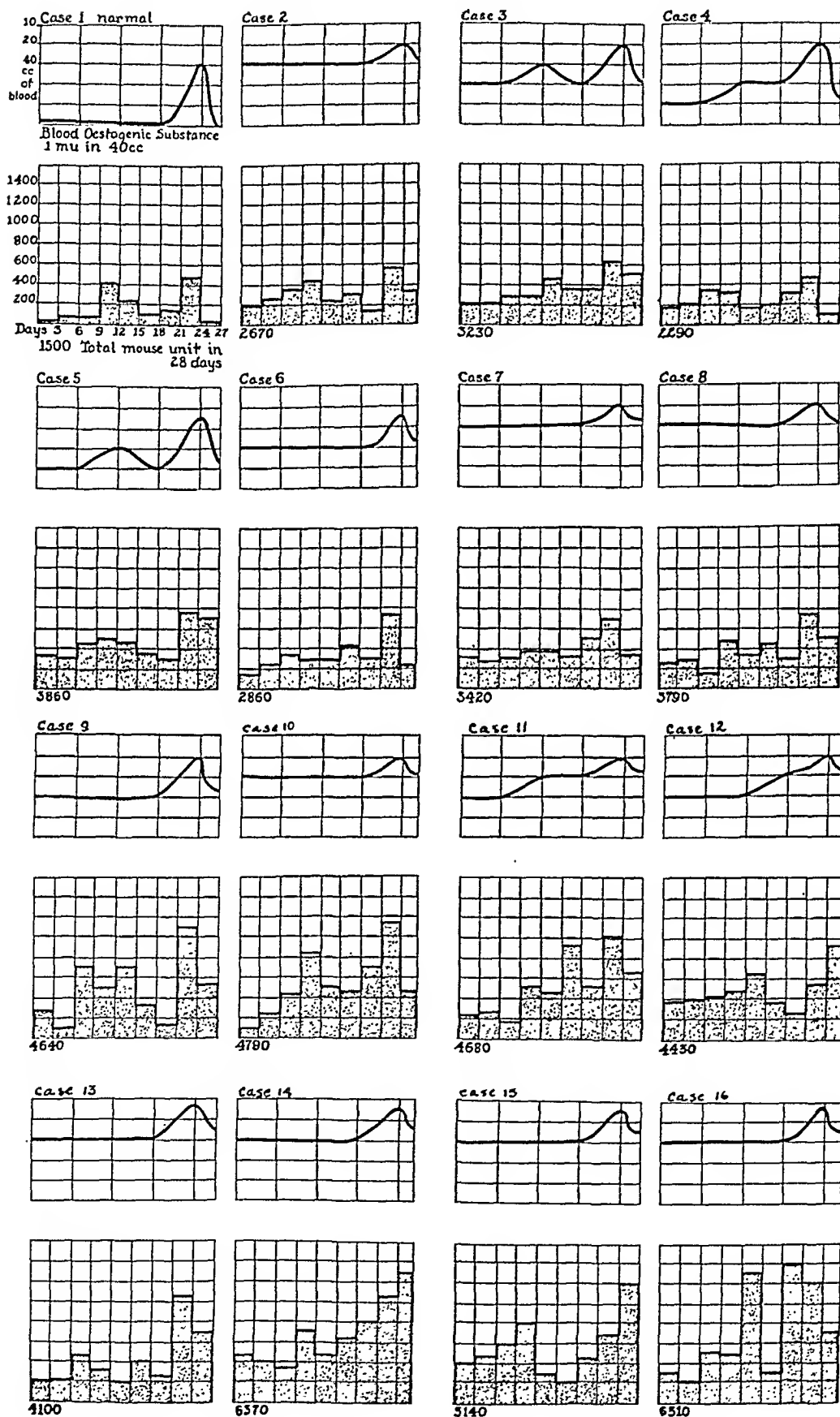


FIG. 2.

studies were made within five days of the onset of the menstrual flow. Of these 42 gave strong positive reactions, 24 gave normal positive reactions, and 4 weak positive reaction. These results seem to corroborate the findings of Groups I and II.

As to the cause of this excessive production of the estrogenic substance, we are unable at the present time to ascertain, since we are unable to make clinical tests for the progesterin content of the blood and urine or blood assays for gonadotropic substance present in amounts less than normal. It seems probable since theelin and progesterin have in many instances antagonistic actions, that this excess of theelin would be accompanied by a deficiency of progesterin which is a type of ovarian failure. That this failure is not primary in the ovary is shown by the fact that the Fluhman test was in no cases positive. Hence, we are dealing with ovarian failure which is secondary in nature, and probably due to insufficient stimulation by the anterior pituitary gland.

We recognize that this excess of estrogenic substance in the blood and urine is not a unique finding: that it also occurs in certain types of amenorrhea, in functional bleeding, and in greatest quantities in pregnancy. We believe that it is not so much the actual amount of theelin present in any of these conditions as it is the theelin-progesterin ratio which determines the clinical manifestations of the glandular disorder. The maintenance of the normal ratio is in turn dependent on the proper function of the pituitary gland.

Novak and Reynolds,² by a very ingenious method, have demonstrated that, in the rabbit, regular rhythmic contractions of the uterus occur, which disappear after castration and are restored by the administration of theelin. Also, that these contractions, excited by the administration of theelin, are depressed very markedly by the administration of progesterin or prolan.

The pain of menstruation is usually of a sharp cramping nature, which may very well be due to excessive uterine contractions. For proof that strong uterine contractions cause pain, it is only necessary to mention the pain which is incident to labor almost without exception.

It is upon these findings that we base our concept of dysmenorrhea, namely, that it is due to a type of ovarian failure, secondary to anterior pituitary hypofunction usually, in which there is an excess of theelin and a deficiency of progesterin, which disturbed ratio causes excessive uterine contractions which are painful. Upon this concept a routine of treatment was outlined and applied.

In selecting cases of functional dysmenorrhea for study the following classification was used:

I. Dysmenorrhea caused by Organic Pathology

1. Pathology of the genital organs
2. Constitutional abnormalities
3. Combined local and constitutional abnormalities

II. Dysmenorrhea caused by Functional Pathology

1. Nonendocrine causes

- a. Pelvic congestion
- b. Allergy
- c. Neurosis

2. Endocrine causes

- a. Ovarian dysfunction, primary
- b. Ovarian dysfunction, secondary
 - (1) Hypopituitary function
 - (2) Hypothyroid function

A correct classification is essential. It is the first and most important step in treatment, for, unless it is done properly, results of therapy will be only what could be expected from any "hit-or-miss" method. First, organic causes must be ruled out. This is not always easy, for often pelvic pathology is present which cannot be detected by pelvic examination. After the case is established as functional in origin, the type must be differentiated. We have recognized four types; of the nonendocrine causes, pelvic congestion is probably the most important. Neurosis, though considered in the past as the basis of many cases of dysmenorrhea, probably accounts for few, if any, cases. However, the mental and emotional status of the patient is very important. Allergy may account for an occasional case.

Finally, on establishing the case as endocrine in origin, two more questions must be answered: What gland or glands are involved and to what degree? and, are contributory causes such as pelvic congestion, anemia, poor general physical condition, or emotional instability present? When these steps have been carefully taken, then and only then can endocrine therapy be applied with any hope of success. Our routine of study for purposes of diagnosis and classification of cases consisted of the following procedures:

1. Complete history and physical examination
2. Vaginal or, in the virgin, rectal examination
3. Urinalysis
4. Hemogram
5. Basal metabolism rate
6. Hormone study
7. Blood chemistry, in selected cases
8. X-ray of the sella turcica, in selected cases.

By such a study, sixty cases were selected as suitable for endocrine therapy. The methods used and the results obtained are summarized in Table I. These cases have been observed for periods ranging from six months to three years, the majority having been treated more than one year ago. Of the 60 cases 53, or 88 per cent, were relieved, 6, or 10 per cent, were improved and 1, or 2 per cent, received no benefit from the treatment.

Based on the concept that dysmenorrhea may be due to an imbalance between theelin and progestin production, therapy should be directed toward a reestablishment of the normal ratio of these hormones. Theoretically, this could be accomplished either by supplying the deficient hormone or by stimulating the glands to secrete normally. Organotherapy constitutes the first method, and we believe that x-ray accomplishes the second.

TABLE I. RESULTS OF TREATMENT OF SIXTY CASES OF FUNCTIONAL DYSMENORRHEA

	TOTAL NUMBER OF CASES	RESULTS			CASES ALSO GIVEN THYROID			
		RE- LIEVED	IM- PROVED	FAILURE	TOTAL	RE- LIEVED	IM- PROVED	FAILURE
Antuitrin-S	13	12	0	1	5	4	0	1
Proluton	14	12	2	0	2	1	1	0
X-ray to pituitary	5	44	1	0	3	2	1	0
X-ray and antuitrin-S	21	20	1	0	12	12	0	0
X-ray and pituitary	7	5	2	0	4	4	0	0
Total	60	53	6	1	26	23	2	1
Per cent		88	10	2	44	38	4	2

In the use of organotherapy in the treatment of dysmenorrhea several products are to be considered, namely, the anterior pituitary-like hormone of pregnancy urine, the luteal hormone, thyroid, and theelin. The anterior pituitary-like hormone marketed under the names of antuitrin-S (Parke, Davis Co.) follutein (Squibbs), anterior pituitary luteum (Harrison, McKenna, Ayerst) is of questionable value, since it is doubtful whether this substance actually stimulates the human ovary to corpus luteum formation. Theoretically, the anterior pituitary luteinizing hormone has a restorative effect as far as the ovary is concerned, stimulating it to produce its own hormone, but it is substitutional as far as the pituitary is concerned. Hence, if the fault lies in the pituitary, this substance would be effective only as long as administered. In some cases, however, it seems that after the readjustment is made, the glands are able to maintain their balance and the disturbance does not recur. We used antuitrin-S with some success in the earlier part of our study before the luteal hormone became available commercially. Wither-³ and Brown⁴ have reported on relief of dysmenorrhea by the use of the urinary gonadotropic substance.

The luteal hormone is marketed as proluton (Schering, in strengths of $\frac{1}{25}$, $\frac{1}{5}$, 1, 5 international units) and as progestin (Upjohn). We have recently been using proluton, but purely as a temporary measure, since it is substitutional in its effects and cannot be expected to effect a permanent cure. It is given beginning two weeks preceding the expected period in doses of 1 c.c. containing one international unit, every other day up to the onset of the period. In severe cases the 5 interna-

tional unit strength is used and is continued throughout the period. This schedule is repeated for three months. The patient is told not to expect any results until the third period after the treatment is started.

Thyroid, when indicated, is a helpful agent. Theelin is definitely not indicated in the treatment of dysmenorrhea, except perhaps in the presence of an infantile uterus and even here the deficiency is better corrected by the stimulation of the pituitary gland. While we used theelin in some of our earlier cases, the amount then available was so small that we feel that it was quite ineffectual. Israel⁵ found that gonadotropic and estrogenic substances were both ineffectual when used as the only means of treatment of dysmenorrhea.

The use of the x-ray to the pituitary gland⁶ in functional disorders of the female was introduced by Hofbauer before the German Gynecological Congress in 1922.

Rubin⁷ in 1924 used x-ray therapy to the ovaries and later to the pituitary gland in cases of functional sterility. Ford⁸ and Dripp of the Mayo Clinic found irradiation helpful in relieving symptoms associated with the menopause and reported relief in 18 patients out of 29 cases of dysmenorrhea so treated. Newell and Pettit⁹ reported relief of 72 to 82 per cent of cases of dysmenorrhea treated by pituitary irradiation.

The medical profession, as a whole, has been slow in accepting irradiation of the pituitary gland for functional disorders of the female. It is still being regarded as a destructive agent. Given in fractional doses in those cases in which it is indicated, it is, in our opinion, far more beneficial in the correction of functional disorders of the female than any endocrine preparation now available. The technique for x-ray therapy as described by Christie¹⁰ is as follows:

"20 milliamperes, 200 K.V.P., 5 minutes, 60 inches distance, $\frac{1}{2}$ mm. copper and 1 mm. aluminum filter (170 'r.' units) to right and left sides of the pituitary gland every three weeks for four treatments. At the end of this, patients may return in two months and another series may be given if necessary."

To summarize the treatment which we have employed in cases of dysmenorrhea, the following measures are used: (1) Instructions in general hygienic measures, (2) tonic when necessary, (3) thyroid when indicated, (4) proluton as outlined above, and (5) x-ray to the pituitary gland.

CASE REPORTS

CASE 1.—Mrs. M. F., aged twenty-seven. This patient was first seen May 7, 1935, complaining of severe dysmenorrhea which started after her marriage four years previously. Her past history was essentially negative. Menstruation started at the age of fifteen years, each period lasting four days, normal in amount, and occurred every twenty-six days. Pain, of abdominal cramping nature, started two days before the onset of the flow and was accompanied by considerable breast tension and at times marked skin eruptions and headache. It was necessary for her

to remain in bed. She had never been pregnant. Physical and pelvic examinations were negative. Basal metabolic rate was minus 8; urinalysis, negative; Hb. 78 per cent, R.B.C. 3,250,000, and W.B.C. 8,100.

Treatment consisted of x-ray to the pituitary gland June 20, July 11, and Sept. 16, 1935; thyroid gr. $\frac{1}{2}$ t. i. d.; proluton as outlined above, for three months; iron ammonium citrate. The patient has been greatly relieved for the past twelve months. She no longer needs to stay in bed at her periods but occasionally takes a pyramidon tablet.

CASE 2.—Mrs. D. H., aged twenty-four, was first seen June 1, 1934, complaining of dysmenorrhea and irregular menstruation. Her past history was essentially negative. Menstruation began at the age of twelve years, each period lasting seven days and recurring every thirty-two days. She had had no pregnancies. The pain occurred about two days before onset of the flow, at times being so severe that she had to go to bed. It was accompanied by severe headaches and acne. Examination revealed her to be of the infantile type, being six feet three inches tall and weighing only 107 pounds. Breasts were small, hips narrow, uterus infantile. Basal metabolism rate was minus 21; urinalysis, negative; Hb. 74 per cent, R.B.C. 3,700,000, and W.B.C. 8,400.

Treatment consisted of: thyroid, gr. 1 t. i. d.; antuitrin-S given for one month and proluton the following two months; x-ray to the pituitary gland June 11, July 2, and July 23, 1934. Since completion of the treatment, this patient has had regular periods with no pain.

CASE 3.—Miss H. D., aged thirty-two years, was first seen Aug. 28, 1935, complaining of severe dysmenorrhea, backache, and headache. Aside from an automobile accident in 1931, her past history was essentially negative. Menstruation began at the age of fifteen years, each period lasting ten days and recurring every twenty-eight days. In the past few years the flow had lasted only eight days and had been less profuse than at the onset. The flow was preceded by about two days of nausea and vomiting, breast tension, headache, and acne on the face. Pain occurred on the first day of the flow. Examination revealed the patient to be infantile in type with small breasts, flat hips, and infantile uterus. The basal metabolic rate was plus 2; urinalysis, negative; hormone test, strongly positive blood estrin and negative pituitary; Hb. 80 per cent, R.B.C. 4,020,000, and W.B.C. 7,800.

Treatment consisted of x-ray to the pituitary gland on the following dates: Aug. 23, Sept. 23, and Oct. 15, 1935. Proluton in one-fifth rat units every other day in the two weeks preceding menstruation for a period of three months. The patient is greatly improved. She has had no nausea and headaches since the treatment and the pain is very mild.

CASE 4.—Miss C. G., aged thirteen, was first seen July, 1934, complaining of severe dysmenorrhea. Her past history was essentially negative. Menstruation started at the age of twelve years, each period lasting four days and recurring every twenty-eight days. Pain was present during the first part of the period making it necessary for her to remain in bed for at least one day. General examination was negative; a pelvic examination was not made. Basal metabolic rate was minus 4; urinalysis, negative; Hb. 70 per cent, R.B.C. 3,600,000, and W.B.C. 12,050; blood hormone tests, strongly positive estrin and negative pituitary.

Treatment consisted of: Thyroid gr. $\frac{1}{4}$ t. i. d.; antuitrin-S for one month and proluton 1 rat unit for two months as outlined above. This patient is greatly improved. It is no longer necessary for her to spend any time in bed.

CASE 5.—Miss R. P., aged thirteen and one-half years, was first seen June 12, 1936, complaining of severe dysmenorrhea and acne. Her previous history was

essentially negative. Menstruation began at the age of eleven years, each period lasting four days and recurring every twenty-eight days. Since the onset, pain had been so severe that she was obliged to spend at least one day in bed. Physical examination was negative. Basal metabolic rate was minus 29; blood hormone test, normal estrin and negative pituitary; urinalysis, negative; Hb. 80 per cent R.B.C. 4,200,000, and W.B.C. 7,500.

Treatment consisted of: Thyroid gr. $\frac{1}{2}$ t. i. d. for three months. Since that time, this patient has had no menstrual discomfort and the acne is clearing up.

CASE 6.—Miss M. C., aged twenty-six years, was first seen July, 1934, complaining of severe dysmenorrhea. Her past history was essentially negative. Menstruation began at the age of thirteen years, each period lasting seven days and recurring every twenty-eight days. Pain was present throughout the period, clots occurred at times and nausea was also present. Physical examination was negative, except for pelvic congestion. Laboratory findings were also negative. The patient was given Elliott heat treatments to the pelvis over a period of two months. Since then she has felt fine, her periods have been normal without pain or nausea. Endocrine therapy in this case would have been useless.

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Unilateral absence of the uterine adnexa is rare. It occurs occasionally in lower forms of animal life, as, e.g., in the Scolecidae and the Turbellaria. In these worms only the left tube is developed and the right remains as a closed sac. In many sharks, the right tube is atrophied or at least smaller than the left. In certain bony fishes and in many reptiles and especially in birds there is failure of development of the right tube as a rule. In the monotremes this is generally the rule; vultures have both tubes. The cause is not far to seek. In the domestic hen of normal fertility, if there should be maturation of 280 fully developed eggs per year, the pelvis would be constantly occupied by eggs. In the lower mammals and some birds a large egg is produced which is covered by a hard or calcareous shell and surrounded by the tube but in higher mammals the egg is microscopic. In the elephant, e.g., the egg is exactly the same size as in the mouse, both being microscopic. The failure of development of the right tube in higher mammals and in the human being is a throwback to lower animal life.

W. B. SERBIN.

THE STATUS OF PSYCHOTHERAPY IN GYNECOLOGIC PRACTICE

MAX D. MAYER, M.D., NEW YORK, N. Y.

(From the Gynecological Service of the Mount Sinai Hospital)

EVERY medical problem includes a psychologic component, but in certain conditions this plays a larger rôle than in others. The psychologic aspects of gastroenterology, cardiology, and urology are of particular interest. Gynecology is most intimate in its relation to psychotherapy for many reasons. A great proportion of unconscious conflicts deals with sex problems as a result of personal and social restrictions; thus it is not surprising that the genital zone is so often the center of attention and the target of projection. Any existing genital abnormality, dysfunction, or pathologic process is readily over-evaluated.

Anthropology points out the predominating importance of the sexual function in the history of woman. At some of the sexually critical periods in a woman's life we meet with phenomena in which the verification of femininity is associated with bleeding and, often, pain; the onset of menstruation, menstruation itself, defloration, childbirth. The initial realization of sex difference and inferiority attitudes resulting from special circumstances at the time of such realization, have also been emphasized as traumatic. All these factors predispose to a vulnerability in respect to anxiety, the central theme of the neuroses. The cyclical functions are dependent upon glandular control which in turn is sensitive to sympathetic nervous changes, adding to the vulnerability.

It is for these reasons in part, that a large proportion of the patients applying to gynecologists have complaints in which the quantitative distribution of psychic factors makes us focus our attention in their direction. The gynecologist and obstetrician is readily chosen as the father confessor. An initial modesty barrier has been broken down. Transference is easily made. The gynecologist seems to be the logical person to consult in the matters of premarital counsel, marital maladjustment, frigidity, contraceptive problems, and sterility, in association with which there are so many conflicts.

Compared to other specialists gynecologists were not slow to recognize these facts. Some were pioneers in the total personality approach. A certain reluctance among the rank and file may perhaps be accounted for by the unconscious determinants of vocational choice. Additional lag can be attributed to the exigencies of time, the objec-

tion to the possible intrusion of the erotic motif into the consulting room, and the undoubted tediousness of the therapy as compared to surgery.

Soon, enormous clinic material was accumulated, establishing the cogency of acute factors such as for instance, fright, influencing physiologic processes; and of chronic influences, fears, hopes, wishes, suggestions and autosuggestions, leading not only to symptoms but to organic changes as well. These changes involve circulatory redistribution, changes in muscle tonus and in glandular secretion.

In gynecology we deal with these principally in the manifestations of pain, bleeding, and discharge.

Psychotherapy is useful in gynecology in a general sense in all patients, connoting an attitude about the rôle of the illness in the life of the patient and how the physician fits into the picture, and in a specific sense in selected cases. It has forced an increased emphasis on the search for all organic components and for reexaminations to exclude and evaluate them, the search for positive evidence of psychic factors in the personality, heredity, constitution, and biography, and the tertium quid, the linking of such factors to the specific manifestations in a dynamic fashion. Into this framework of psychotherapy, psychoanalysis fits in a threefold manner: As an appreciative basis, as an anamnestic technic, and as a therapeutic technic both in its orthodox form and in the application of its dynamics in nonanalytic therapy.

The symptoms and syndromes to be discussed below are not conceived of as psychic entities; as they are presented to the gynecologist they serve only as convenient points of departure. In reality the only entity is the whole patient, since any of these symptoms may be part of a general psychoneurotic or psychotic disturbance. (For instance, the cessation of menstruation in manic-depressive psychosis.) If this material were being presented to psychiatrists, the emphasis would be upon psychiatric classification.

Some examples of leading symptoms in gynecology which may be more or less influenced by or influence psychic processes are:

Amenorrhea.—1. A girl of twenty-one complained of amenorrhea. Her period was two weeks late; she had always been regular. She was to be married in two weeks. There had been one premarital exposure one month before, with adequate contraceptive precautions. Examination showed no evidence of gravidity, the Aschheim-Zondek test was negative. She was reassured and the period came on the next day.

2. A woman of thirty years has been amenorrheic for nine years since an attempt at rape by her fiancé, with whom she quarreled and from whom she separated. This was followed by a depression which lasted for months, which is repeated every year at the anniversary of the incident nine years ago. Hormone studies are completely negative. Investigation showed a cyclothymia and the above superimposed conversion symptom.

3. A woman of thirty-five complained of amenorrhea of six months' duration, with distention of the abdomen, nausea, and vomiting. This was diagnosed elsewhere as pregnancy and finally, as a tumor, for which she was operated upon at a hospital. At the time of operation the uterus was small and nothing was found to correspond to the supposed tumor. This case of pseudoeypsis in a hysterical individual is a gross example, minor forms of which are quite common. In women who have conflicts about childbearing and who are sterile, we frequently see the triad of symptoms of distention, pain under the left breast, and a feeling as if something were moving around in the abdomen. We have seen the complete picture of a false pregnancy coming on postpartum as the first external evidence of a beginning severe manic-depressive psychosis which soon required institutional treatment.

It is clear that amenorrhea may be a symptom of a variety of mental conditions ranging from an acute and temporary fear through various degrees of hysteria to the severest psychosis.

Menometrorrhagia.—There is ample evidence that irregularity in the amount and time of the bleeding may result from mental causes. But here we are treading on dangerous ground. The exclusion feature of the diagnosis is difficult, and it is quite dangerous to neglect early recourse to diagnostic curettage.

The onset of menstruation as well as its cessation is often associated with psychic disturbances. The reaction to the first menstruation will depend upon the entire developmental experience of the girl plus the specific preparation for the event. It is in the prophylactic sphere that the teachings of psychoanalysis infiltrating through all of society, pedagogy, and more immediately, the attitude of the parents, can accomplish most. Superstitions can exert marked and lasting influences. (For instance, the barbaric custom of a sudden slap by the mother at the girl's announcement of the initial bleeding.) We are all aware of the pernicious effect of overcoddling and the invalidism attitude.

At the *menopause* there is a considerable concomitant variation between the severity of the subjective complaints and the degree of maladjustment as discovered by careful investigation. This does not say that the symptoms are invariably psychogenic. The results of psychotherapy, however, when compared in large series of cases are as good as the other forms of therapy. A warning is in order to proceed slowly and cautiously in the psychanamnesis in these women because of depressions, melancholia, etc. In this group with somewhat limited resources for reequilibration, we must be careful not to disturb relatively harmless, sometimes very useful symptoms, since we may break down a defense mechanism and have nothing to offer in its stead. Some of the facts found in disturbances at this period are: the fear of growing old and dying, which is mobilized by the cessation of bleeding; the fear of losing attractiveness, losing the partner, disturbing his potency, and loss of libido; the realization of the impossibility of further childbearing, and the unrealistic, unconscious wish to have more children,

converted into hysterical symptoms, often involving the gastrointestinal tract; ideas of jealousy (paranoid) in which the jealous delusions may be projections of unconscious wishes for infidelity; accentuation of certain attitudes toward the grown children, largely in the service of the wish to keep them young, attached, and interfering with their marriage or leaving the home.

In the surgically or radiotherapeutically induced menopause, much can be done by prophylactic psychotherapy. The effect upon the libido varies considerably and is dependent on individual factors.

Pelvic Pain.—Among the clinical pictures frequently met with in the group under discussion, we include dysmenorrhea, dyspareunia, ovarian neuralgia, some cases of mittelschmerz, and certain paresthesias, of which the most troublesome one is pruritus vulvae. One may also include the right-sided pain often found in young single adolescents, so often associated with a masturbation conflict and so often operated upon for chronic appendicitis.

Dysmenorrhea continues to be a baffling symptom; even when we exclude the women with pelvic tumors, displacements, endometriosis and detectable hormonal disturbances, a great number of sufferers are left. In some of these psychogenic factors are contributory or determining. Before subjecting the severest cases to such operations as sympathectomy, expert psychotherapy is certainly indicated. This is true not only for menstrual cramps, but includes premenstrual vomiting, premenstrual tension or depression. It must be remembered that dread of the ever recurring distress may in itself *lead* to an anxiety state, which adds to the therapeutic difficulties. The generalizations that have been frequently made in regard to masculine protest and penis envy are by no means universally applicable. The results of prolonged mental treatment are, however, very encouraging and often save the patient from operation or drug addiction. Suggestive treatments are almost invariably only of temporary value. This is true of the intranasal treatment as well.

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The majority of cases of dyspareunia coming to the gynecologist are primarily psychogenic, although all cases have some psychologic factors. The more these factors are taken into account, the more efficacious the treatment. One must interview the husband as well, as, obviously, he may be the one who requires attention.

For practical purposes the treatment of psychogenic dyspareunia may be divided into:

A. *Initial dyspareunia* of which there are the mild, the severe, and the extremely severe forms.

1. In the mild type, there is a somewhat excessive reaction to an unfavorable situation, as for instance, an inept, inexperienced hus-

band, an unusually thick hymen, a timid individual; the patient is cooperative and has insight. In these cases the treatment can be rapid and one can very well combine local treatment with psychotherapy. This method embodies the dynamics of the psychotherapeutic cure without any attempt to give the patient conscious insight. In this respect it is similar to many forms commonly used in medical treatment, but differs in that the physician is more aware of the mechanism.

At the first visit the patient is interviewed (mostly listened to) and preferably not examined. When an examination is eventually made, it is but an inspection. There should be no pain. The doctor gets the woman's confidence.

An endoscope is inserted through which a wick of medicated gauze is passed and left in. At subsequent visits very gradual mechanical dilatation combined with the local applications finally permits the easy introduction of the smallest vaginal speculum. This is replaced by a series of graduated test tubes up to $1\frac{1}{4}$ inches in diameter. Then the patient is shown how to introduce this test tube herself, which she does with ease. Then she is given the test tube and instructed to introduce it herself at home for several days. The husband is interviewed and instructed, and all treatment tentatively discontinued before the couple make any attempt at coitus.

The underlying principle is the establishment of confidence and the transference through which the fear, resentment, and anxiety are partially overcome. This permits the alleviation of the local condition by mechanical means which is presently replaced by an instrument with phallic significance. The patient is encouraged to be cooperative in its introduction. The treatment is then terminated and the patient returns to her coital function with an altered point of view. I do not think one need fear the danger of instituting autoerotism principally because these women are not vaginally erotized.

2. In severer cases we see an inadequate response to a not unusual situation. There is no disproportion and there are other manifestations of a neurotic make-up; cooperation is not complete and insight is often lacking. In these cases the approach should be purely psychotherapeutic up to the point where the patient is herself desirous of having local treatment started.

3. In the extremely severe forms, as for instance in the cases of persistent virgins for many years, we must be extremely cautious. They are frequently psychopathic personalities. Interference here is not without considerable danger of a complete breakdown and even suicide.

B. Acquired Dyspareunia.—In the first group resulting from fear of pregnancy one may combine a brief psychotherapy with adequate contraceptive advice. In the group in which the dyspareunia is a result

of a negative reaction against the husband, local treatment is of no avail. Brief psychotherapy of the suggestive type is almost always doomed to failure. Prolonged psychotherapy offers only a reasonably fair prognosis as far as the dyspareunia is concerned. The prognosis is poor in respect to the frigidity.

* * *

Training in psychoanalysis has a triple usefulness in the treatment of these cases: (1) It offers the road to the possible understanding of the complex mechanisms through which these conditions arise. (2) It offers a technic for intelligent listening in the eliciting of an adequate history. (3) In very carefully selected cases, it offers a radical therapy which attempts to combine the removal of symptoms with an adjustment or readjustment of an unhappy individual.

Pruritus Vulvae: Some cases of pruritus vulvae which defy all other means of treatment respond to intense psychotherapy. The approach to these, however, requires as a preliminary an interruption of the vicious circle that scratching produces more pruritus; a temporary alleviation is the entering wedge. Unconscious masturbation in a sexually frustrated individual is, of course, the most common mechanism; yet saying so, bluntly, is of no use and often has unfortunate results.

Leucorrhea: In addition to the cases of leucorrhea due to local and general causes, we find some in which no cause can be found, and there is a persistent thin, mucoid, occasionally even mucopurulent discharge, varying with mental conflicts, influenced by mood changes and eradicable by an attention to the total person. Ungratified instinctual urges, constant daydreaming and turgescence, masturbation conflicts, premature ejaculation on the part of the husband, are some of the things frequently found in these patients. But it is not only in the so-called "fluor albus" that we find psychodiagnosis and therapy necessary. Even in the most specific infections it may sometimes be essential to investigate and treat the mental contributory factors, the perpetuating faulty sex practices and the secondary gains from the illness. For instance, in a series of 100 cases of *Trichomonas vaginalis* vaginitis, the overwhelming majority of the sexually active women had inadequate gratification.

One of the most important groups which includes a variety of links between gynecology and psychotherapy is that of marital maladjustment. This subject has been of major interest in recent years. Many patients come to the gynecologist with overt maladaptations to marriage or with symptoms which are more or less readily reduced to that issue. The gynecologist can accomplish a great deal in certain of these situations, in direct proportion to the extent of his training in psychology. Incidentally, much can be done prophylactically by pre-

marital instruction. Books, no matter how well written, do not begin to compete in value with personal management of these cases.

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In the field of contraception, psychotherapy is of obvious importance. We can touch upon but a few of the many issues that arise. The widespread practice of coitus interruptus is no doubt compatible with mental and physical health in many men and their mates, somewhat dependent upon the degree of control in the case of the man, and the rapidity of orgasm in the woman. On the other hand, it is often associated with disturbances in the form of neurasthenia or psychoneurosis. When long-continued, especially when associated with premature ejaculation, the chronic pelvic turgescence in the woman without deturgescence may result in subjective fullness, pain, dragging sensations, paresthesias, and may actually lead to the objective signs of thickening, shortening, and tenderness of the uterine ligaments. Many of these women can be considerably helped by a change in their contraceptive technic combined with instruction, encouragement and psychotherapy of their partners. Proper contraception is an important factor in many cases coming to the psychotherapist. We must, however, not overlook the fact that the anxiety associated with the fear of pregnancy is *not* always relieved by realistic means and may require extensive further investigation and treatment.

The sterility clinic offers an enviable opportunity to study a large variety of neurotic conditions. In addition to the overt self-evident reasons for concern about sterility, we encounter exaggerations of affect which emanate from ego injuries, from the necessity and impossibility of proving self-doubted femininity or establishing mother identification. Failure to cure sterility, or, in lieu thereof, to adjust by means of adoption or substitutive gratifications, may result in tragic consequences. Many of our cases of cancerophobia are recruited here, for reasons every psychiatrist will gather. The function of the gynecologist, then, does not end when he is confronted with a hopeless prognosis.

Frigidity, from the gynecologic standpoint, can be divided into the primary and the acquired types. The prognosis is far better in the latter group. The situation is complicated by the fact that we are dealing with two protagonists, often with two neuroses that do not dovetail. The principle in therapy is a judicious retracing of the preceding life situations as far as is necessary. The prognosis must be cautious and radical psychotherapy should be instituted only after the most mature deliberation.

Frequently, we find marriages in which one or both partners have latent homosexual trends. These marriages may have compensatory values. Great care must be exercised in case management not to disrupt a marriage needlessly.

The endocrinologic aspects of gynecology are also rich in psychologic problems. We see here profound injuries to self-esteem, in cases of obesity, hirsutism, and distortion of body proportions. There are feelings of inferiority consequent on lack of femininity or its accepted standards and difficulties, arising from lack of attractiveness and delay or impossibility of marriage. The same is true of congenital gynecologic abnormalities. The most notable example is absence of the vagina, in which the necessity of a construction of a vagina is of individual, rather than social importance. We have seen splendid examples of complete adjustment in previously very depressed individuals following the Frank-Geist operation for absent vagina, though it is true that a temporary adjustment may merge into a later breakdown because of the absence of children.

Certain examples from the field of obstetrics require mentioning. In the vomiting of pregnancy we have an example of an intricate interlacing of conscious and unconscious mental factors with nervous, hormonal, and chemical ones. Clinical data point to its greater frequency when a conflict in regard to childbearing is present or where there are antagonistic attitudes toward people in the environment. In the choice of obstetric analgesia, the modern obstetrician individualizes according to the psychologic need of the patient in preference to proceeding by any rule of thumb.

The mental attitude toward nursing a baby is also subject to considerable variation. Insight into the causes of objections to it and patient discussion will do much to alter an all too prevalent attitude.

It may be misleading to lay too much emphasis on presenting symptoms; in the majority of instances it will soon be evident that the chief complaint is only one of a large number that may appear one after another, or in groups. Often we can derive the common denominator to see the usefulness of the symptoms to the patient and understand how they all defend against a single threat and thus get an insight into the basic anxiety. In a psychoanalysis the focus of attention shifts rapidly from the single symptom to the total personality.

Experience in this type of work and extensive contact with the actual treatment of neurotic women will permit the physician to make certain important immediate decisions and avoid certain pitfalls. Automatically he asks himself, "Is the complaint really explained by the organic findings? If not, is it connected with a psychic situation? Is this within the realm of accessibility to me or to some one else? What resources are there for adjustment? What methods are there at my disposal?" As a corollary of this, he automatically classifies the conditions into those that are organic from the practical standpoint, organic with a psychic utilization, primarily psychic with or without organic consequences. Furthermore, he will group the cases into those that are (1) mild and recent, amenable to simple therapy

which is directed to an adjustment to, a reconciliation with, or an alteration of, the environment, or to reassurance. (2) More serious psychoneuroses, amenable to psychotherapy in the hands of a trained person, or not at all amenable. (3) Psychoses in which insight is partly or totally lost.

There is a great need as well as great difficulty to put the case into very simple words. This involves the danger that in so doing we forget that the problems presented are not really simple. Perhaps the following statement is oversimplified: confronted by a contemporary problem the patient finds a difficulty. The normal pleasurable satisfaction not forthcoming, the frustration leads to anxiety. The result varies with the vulnerability of the person and depends on the physical and the mental make-up and biography. Previous patterns of behavior determine the choice of the defense against suffering. These defenses vary from the crystallization into a character type to all degrees of flights into illness, even to suicide.

Our function then, according to this statement, would be to study and understand contemporary problems which subjects find difficult, to know what is normal pleasurable satisfaction, what causes their frustration; to understand manifestations of anxiety, the factors making for individual vulnerability, and to be able to evaluate biographic facts. In addition, he must know the usual patterns of behavior, the common defenses, and be able to comprehend the end-results, such as character types and flights into illness. Such an approach requires, in addition to training in all of the social sciences, the patience to "project one's mind over considerable period of time."

In the out-patient department we have had the opportunity to investigate a large number of cases of incontinence of urine. We have been thoroughly impressed that in those cases without cystocele and with negative cystoscopic findings, a psychogenic factor is frequently present. This opinion has been reenforced by the relatively poor results of various forms of operative intervention in such women. Correspondingly gratifying results have been obtained with psychotherapy in these patients, at least half of whom have been relieved of this symptom. It is hardly feasible to enter into the psychic mechanisms at this time. In passing, it may be mentioned, however, that attitudes of spite, resentment, and masculine protest are common. For example, a young woman who had suffered from nocturnal enuresis up to the time of her marriage was completely relieved of this symptom with the establishment of satisfactory sexual relationship. Following a frigidity which was acquired later, she developed urinary incontinence which in turn disappeared with the cure of the frigidity.

There are definite differences in the practical application of psychotherapy and psychodiagnosis in private practice, the clinic, wards, and consultation service. In clinic practice emphasis has been pri-

marily on diagnosis and the therapies used have been in the direction of adjustment, suggestion, modification of the environment and a considerable utilization of assistance of the psychiatric social service department. In clinic practice such assistance is practically indispensable. A close cooperation between medicine and social service is of the greatest value to both. There are clear-cut limitations to the amount of time at our disposal with these patients since the number of such patients is enormous and properly trained assistants relatively few. On the wards, a somewhat more intensive observation is feasible. There is considerable evidence in favor of the value of a routine psychanamnesis of all ward cases, because exterior calm and complete cooperation with the ward procedure may easily mask a really important neurosis. We cannot rely on surface phenomena.

Even if the psychologic investigation as such is not routinely done, it would be quite possible to improve upon the routine histories taken, to fill in certain clear-cut deficiencies. Internes and residents could very well be instructed to add such details as the developmental history with emphasis on chronologic sequence and an attempt to see the relationship of events, such as illnesses, to the adjustment of the patient's life. In addition, greater emphasis could be placed on the marriage relationship, the question of coitus, contraceptives, etc. It takes relatively little time to add a brief outline of the patient's background, schooling, hobbies and resources, her attitude to children, etc.

In the consultation service it goes without saying that psychologic investigation is of paramount importance. Here we deal with obscure cases, a much larger percentage of which have no obvious organic findings. In this group there is an excellent opportunity of testing out the diagnostic value of what can be called the "one-hour interview." Though it has distinct limitations and in spite of the fact that later interrogation may alter, discount, even completely reverse the result of some first interviews, on the whole this plan has been found extraordinarily useful and in trained hands an amazing amount of information can be elicited in this single interview. This is often enough to clinch the impression of a psychogenic disorder and to point the way to an appropriate psychotherapy. It is thus not time-consuming in proportion to other forms of medical investigation.

* * *

Objections have been raised against psychotherapeutic treatment by the doctor who treats organic ills as well. Some of these are valid. It is difficult for a busy physician to spend the necessary time for the special study required in preparation and for treatment. Furthermore it is inadvisable to be in the position to be consulted about intercurrent medical conditions as these are so readily utilized for purposes of resistance, and to gratify unconscious wishes for physical

contacts. It is hard to maintain the necessary impersonal note. This split, however, can be exaggerated into fanaticism. In all psychotherapy short of formal analysis, the difficulties are relatively slight. As a matter of fact an intimate knowledge of both fields is of advantage in case control and avoids the danger of overlooking the significance of important intercurrent symptoms. It is only in formal psychoanalysis that the adherence to a sound orthodox technic makes it necessary to adhere to the rule not to examine the patient after an analysis has been started, and to summon the assistance of a colleague for such check-up examinations as may prove necessary.

When we ask ourselves what we can do for these patients, I am opposed to the point of view that a case is either organic or a case for analysis. There are a number of agents at our disposal. We can lessen the load, organic or mental, or both; we can give sympathy, support, and a point of orientation; we can tend to modify the environment, if necessary with the assistance of social service; we can assist in the acceptance of reality; we can try to remove or alleviate anxiety; we can build up general resistance, strengthen the ego to compensate for frustrations, and we can use the various forms of symptomatic and suggestive therapy in cases that do not lend themselves for obvious reasons to formal psychotherapy. Such suggestive therapy is used in conjunction with the use of local treatment such as pessaries, hydrotherapy, etc., or general treatment with so-called placebos. The judicious use of sedatives when indicated is of considerable importance. We should give attention to the timing of such sedation with due reference to the question of depression, or agitation and insomnia.

The gynecologist, then, should know psychotherapy for the following reasons:

1. To be able to elicit a psychanamnesis.
2. To avoid certain difficulties in the case management of sick women.
3. To know when to supplement his gynecologic therapy with psychotherapy.
4. To use the latter prophylactically, as in premarital instruction.
5. To understand the dynamics of many of his medical and surgical cures.
6. To know when and when not to recommend formal psychotherapy such as analysis.
7. To know when to avoid the subject.
8. To know more about himself.

PARAMETRIAL FIXATION OPERATION FOR UTERINE PROLAPSE

TECHNIC AND REVIEW OF 254 CASES

UDALL J. SALMON, M.D., C.M., NEW YORK, N. Y.

(From the Gynecological Service of the Mount Sinai Hospital)

THE surgical treatment of uterine prolapse is a subject of perennial interest to the gynecologist. For in spite of the fact that several operations have been devised for the cure of prolapse, the most widely used procedures which have given the best results have the objection that they necessitate either removal of the uterus or sacrificing the function of the vagina. Thus, while vaginal hysterectomy or colpectomy will cure uterine prolapse, the usefulness of these procedures is confined to a comparatively small group of patients in whom the uterus and vagina play neither a physiologic nor a psychologic rôle. And, inasmuch as the majority of patients with uterine prolapse fall within the sexually active age group, a plastic procedure, to be of wide applicability for the cure of prolapse, should not entail the loss of the uterus and should not compromise the function of the vagina as a coital organ. If, in addition, the procedure were entirely vaginal and did not require laparotomy for some form of ventrofixation or suspension, it would fulfill the theoretical requirements of the ideal operation, viz., physiologic as well as anatomic restitutio ad integrum with a minimum of surgical risk.

This communication concerns itself with the description of such a procedure and a review of 254 cases of prolapse treated by this method.

HISTORICAL

The combined operation of amputation of the cervix and anterior and posterior colporrhaphy for the cure of prolapse was first performed by Donald of Manchester in 1888.³ While this procedure was subsequently used widely in England and was apparently the only procedure employed for prolapse on Donald's service, he did not publish his technic until 1921.¹ However, Fothergill,²⁻⁴ a pupil of Donald's, described the operation with slight modification in 1908. Subsequently, Shaw^{5, 6} published the technic of the so-called "Manchester operation" as employed at the St. Mary's Hospital, Manchester, England, where the operation was first performed by Donald. A procedure somewhat similar in principle was employed by Halban and described by Mestitz in 1932.⁷ In 1932 Robert T. Frank⁸ introduced a modification of the Donald operation at the Mount Sinai Hospital. In 1935 he reported a series of 106 cases and suggested the name "parametrial fixation" for the operation.

TECHNIC OF OPERATION

The patient is placed in the lithotomy position, is catheterized, and the vagina is scrubbed with green soap and water. The cervix is grasped with a vulsellum

and the cervical canal is thoroughly dilated. A curettage is performed routinely. Fig. 1 illustrates the incisions made in the anterior vaginal wall beginning one inch below the urethral meatus. The incisions are carried downward and laterally circumscribing the cervix on each side at a distance of about two inches proximal to the external os (Fig. 2). The size of the triangular denudation is determined by the size of the cystocele, and the level at which the incision circumscribing the portio is made, is dependent upon the length of the cervix, the extent of the prolapse, and the degree of redundancy of the mucous membrane of the fornices. The triangular mucous membrane flap over the cystocele is then dissected from the underlying fascia and the lateral flaps of vaginal mucous membrane are then freed widely on each side, exposing the subjacent pubocervical tissues. The cut edges of the mucous membrane on each side of the cervix are freed laterally toward the lateral

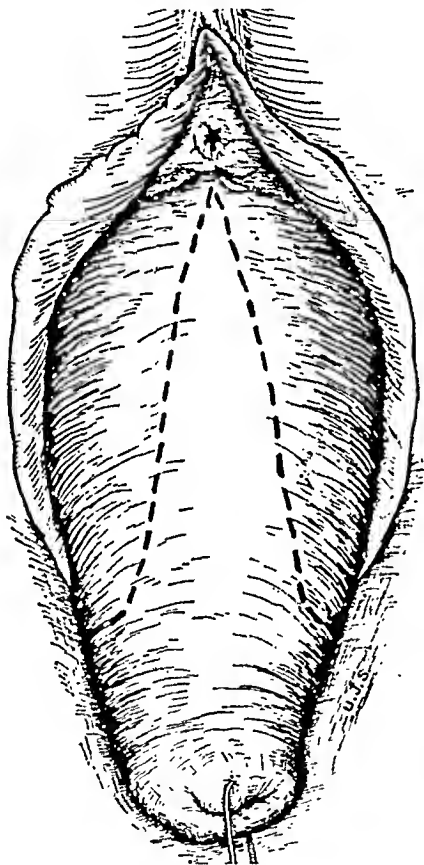


Fig. 1.

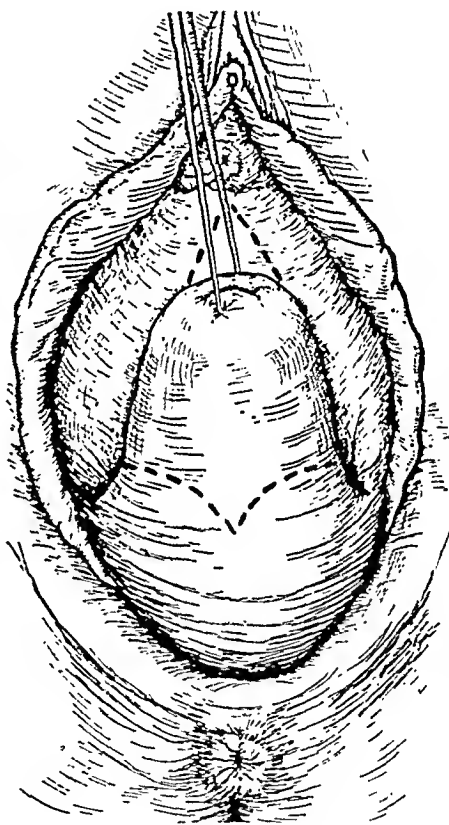


Fig. 2.

Fig. 1.—Anterior triangular incision, starting one-half inch below the urinary meatus.

Fig. 2.—Posterior incision circumscribing the cervix.

fornices, exposing the underlying parametrial tissues and their attachment to the cervix. Posteriorly the mucous membrane is mobilized in a similar fashion, bringing into view the uterosacral ligaments. The parametrial tissues surrounding the cervix at about the level of the internal os are thus exposed on all sides. [Not infrequently during the process of mobilizing the mucous membrane posteriorly the peritoneal reflection of the culdesac is encountered. When small in extent, it is freed from the cervix and pushed upward. When very redundant, to all purposes really an enterocele, the sac is opened, the redundant peritoneum resected, and the opening closed with a purse-string suture attaching the peritoneum to the posterior surface of the uterus above the level of the internal os. This is ordinarily performed after the amputation of the cervix (*vide infra*)]. The lower margin of the

bladder is then defined by introducing a sound into the bladder. The vesicocervical tissue attaching the bladder to the cervix is incised in the midline and the bladder mobilized in the midline in an upward direction. The pubocervical fascial bands (bladder pillars) usually stand out clearly at this point. It is important at this juncture to free the bladder widely in the lateral directions from beneath the pubocervical tissues. This step is particularly important in the cases where there is a large cystocele.

Fig. 3 portrays the bladder freed from its attachment to the cervix and the bladder pillars defined. The bladder pillars are then ligated and severed from their attachments to the cervix on each side. Not infrequently the descending branch of the uterine artery is exposed lying in the tissues underneath the severed bladder pillars. This artery is ligated as indicated in Fig. 4.

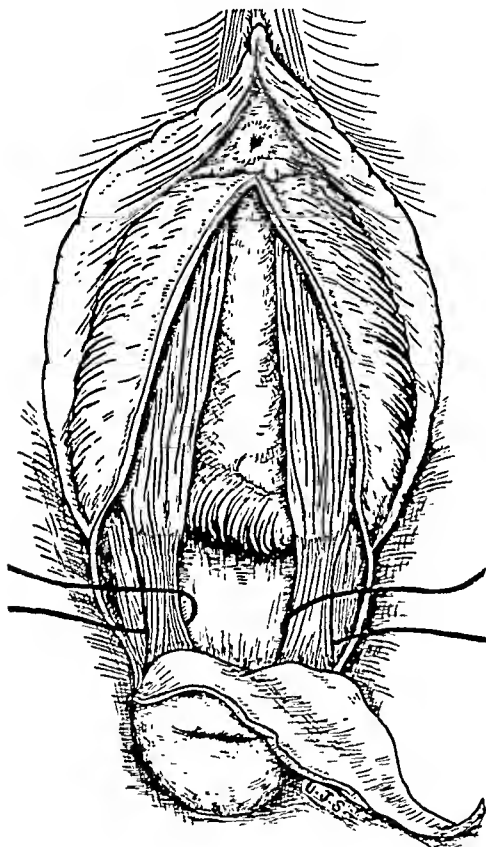


Fig. 3.

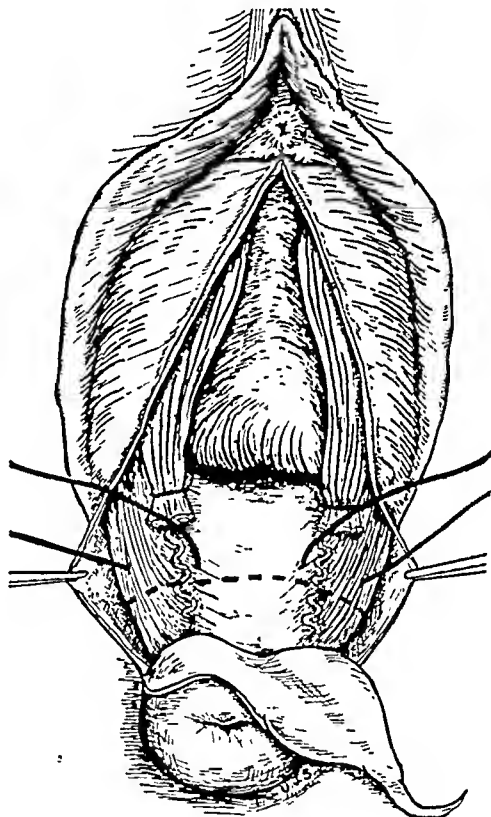


Fig. 4.

Fig. 3.—Triangular mucous membrane flap dissected free. The bladder is freed in the midline from its attachment to the cervix and mobilized in an upward direction. Pubocervical bands (bladder pillars) are then ligated.

Fig. 4.—Pubocervical ligaments ligated and cut, exposing the cervical branches of the uterine arteries. The base of the cardinal ligament on each side is exposed and the vessels are ligated as indicated together with the parametrial tissue close to the cervix. Level of amputation indicated by interrupted line.

In cases of complete prolapse where the parametria are unusually lax, the cardinal ligaments are ligated and severed from their attachment to the cervix at the same time that the vessels are tied. This ligation of the base of the parametria is done only in those cases in which the prolapse is of such extent that the parametria (with traction on the cervix) descend for a distance of one or more inches beyond the introitus. In the average case, however, of first- and second-degree prolapse, ligation of the parametria is not necessary.

Amputation of the cervix is then performed distal to the point of ligation of the vessels. In cases of complete prolapse where the cardinal ligaments have been ligated, the amputation is performed at a high level, immediately below the point of ligation of the parametria (Figs. 4 and 5).

In Fig. 5 are shown the ligated parametria and vessels on each side with the cervix amputated. At this point an anterior colporrhaphy is performed, according to the technic described by Frank,⁹ to correct the cystocele. The pubocervical ligaments are approximated with a No. 3 chromic suture which is passed transversely through the anterior wall of the cervix in the midline. In cases of third-degree prolapse where the cervical amputation is performed very high, this suture is passed through the anterior wall of the uterus. The pubovesical fascia is sutured in the midline with interrupted chromic sutures.

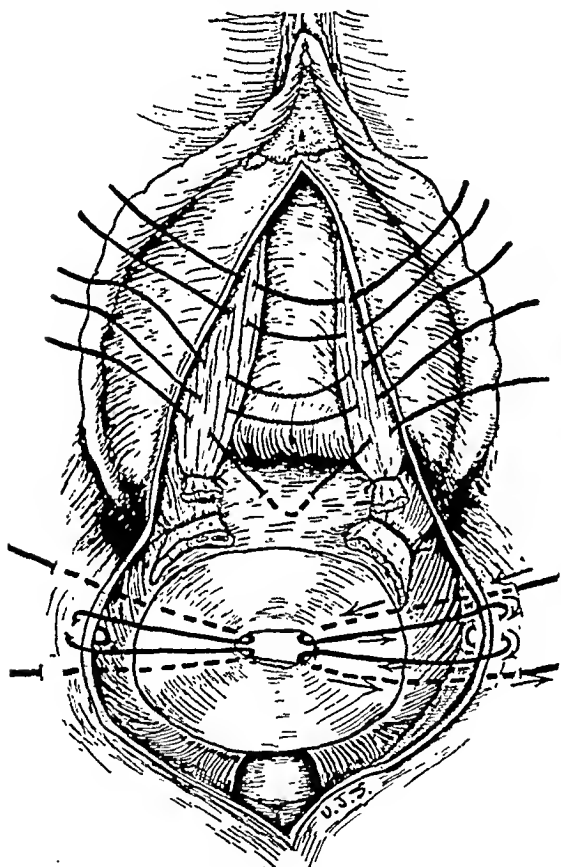


Fig. 5.

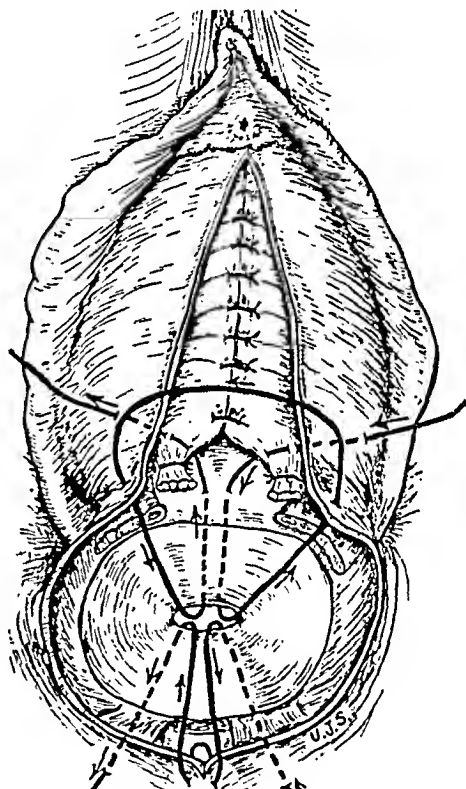


Fig. 6.

Fig. 5.—The cervix has been amputated. The cystocele is repaired by suturing the pubocervical fascia as shown. The lateral parametrial fixation sutures are passed as indicated.

Fig. 6.—The anterior fixation suture is shown traversing mucosa, pubocervical ligaments, and cervix. The posterior fixation suture as illustrated includes mucous membrane, uterosacral ligaments, and cervix. (In order to avoid confusion the lateral fixation sutures are not shown in this illustration.)

The lateral parametrial fixation sutures are then introduced, one on each side, as illustrated in Fig. 5. This suture is started in the mucous membrane of the lateral fornix at a distance of approximately one and one-half inches from the cut edge. The suture is carried through the base of the cardinal ligament and through the lateral wall of the cervix, the needle being brought out through the cervical canal. A bite is then taken in the mucous membrane flap close to the cut edge and the suture is then carried through the cervical canal traversing in reverse fashion the lateral wall of the cervix and the cardinal ligament and piercing the mucous

membrane at a distance of about one inch below the point of entry of the suture (Fig. 5). A similar suture is introduced on the opposite side. Posteriorly, as indicated in Fig. 6, another suture is passed traversing in similar fashion the mucous membrane of the posterior fornix, the sacrouterine ligaments, and the cervix.

The last fixation suture to be passed is the anterior one (Fig. 6). It is started by passing the needle through the lower part of the left anterior flap of mucosa at a distance of approximately one and one-half inches from the cut edges. The lower end of the unattached left pubocervical ligament is grasped and the needle is made to penetrate the cervix, close to the midline at a distance of about one to one and one-half inches proximal to the amputated surface of the cervix. The suture is brought out through the cervical canal and then pierces the deep surface of the mucous membrane flap close to its edge, at the point of junction of the vertical and horizontal edges of the flap. The suture is then carried across the

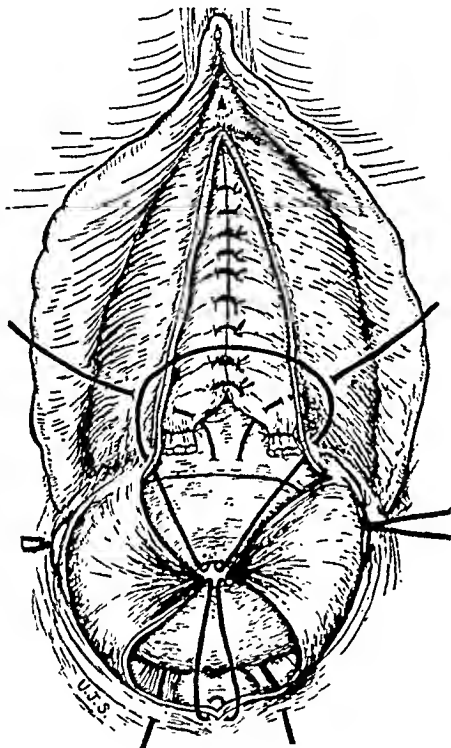


Fig. 7.

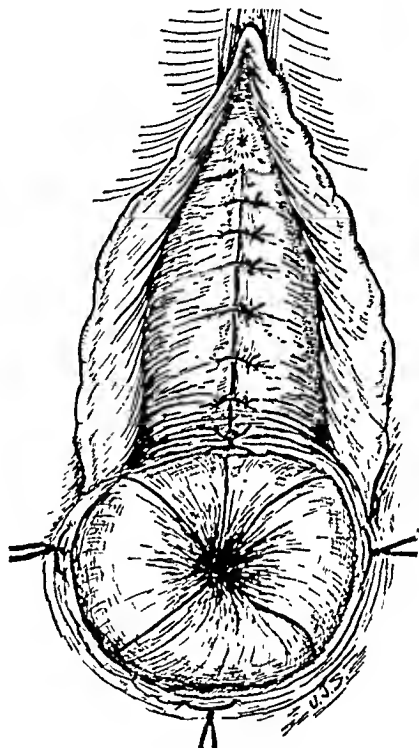


Fig. 8.

Fig. 7.—The lateral parametrial fixation sutures have been tied, resulting in inversion of the lateral mucous membrane flaps.

Fig. 8.—The anterior and posterior fixation sutures are tied and the anterior mucous membrane flaps are then sutured. When completed, the stump of the cervix becomes retracted out of view in the original vault.

midline to the flap on the opposite side and the mucous membrane is traversed from its external surface close to its edge at a point corresponding to the left side. The needle is then introduced into the cervical canal, the anterior wall of the cervix is pierced at a point close to the midline (about one-half inch to the right of the point at which the cervix was penetrated by the entering suture). The suture then picks up the lower end of the right bladder pillar and is passed through the under-surface of the right mucous membrane flap at a distance of about one and one-half inches lateral to the cut edge and an equal distance from the lower edge.

The lateral sutures are then tied. This causes the mucous membrane flaps as well as the lateral parametria to be turned in toward the cervical canal (Fig. 7). The posterior and anterior sutures are then tied in the order named. This results

in complete covering of the amputated cervix with mucous membrane. The lateral flaps of mucous membrane of the anterior vaginal wall are now sutured (Fig. 8). A narrow strip of iodoform gauze is inserted into the cervical canal. A posterior colporrhaphy is then performed. The vagina is packed with iodoform gauze.

In the cases with urinary incontinence, a modification of the Kelly urethroplasty is performed at the time of the anterior colporrhaphy.

STATISTICAL STUDY

Age.—The ages varied from twenty-one to sixty-nine years, the average being forty; 11 patients were under thirty. Eighty-nine of the patients had passed the menopause. (Eight had had antecedent abdominal hysterectomies.) No significant abnormality in the menstrual histories was noted.

Classification.—First degree prolapse: Patients in whom the cervix, on straining, descended to the introitus. Second-degree prolapse: Where the cervix protruded for a distance of at least one and one-half inches beyond the introitus. Third-degree prolapse: Where there was complete descent of the uterus and the fundus, on straining, could be felt at the introitus or below it.

The series consists of 126 cases of first-degree prolapse, 85 of second degree, and 35 of third degree. There were 8 cases of complete prolapse of the cervical stump (posthysterectomy).

The size of the cystocele and rectocele in the individual cases varied widely. The technic, however, was not varied significantly except in 4 cases complicated by the presence of enterocele.

In 2 cases uterine myomas were removed at the same time and in 15 the fallopian tubes were ligated through the vaginal route.

Previous Operations.—Nineteen patients had had antecedent operations for prolapse: anterior and posterior colporrhaphy combined with ventrofixation, 7 cases; anterior and posterior colporrhaphy, 9 cases; interposition and colporrhaphy, 2 cases; hysteropexy and the Polk repair, 1 case. All of these patients had marked prolapse in addition to cystoceles and rectoceles. (In four cases the prolapse was of the third-degree type.) It was difficult to ascertain the exact pelvic status before the primary operation since only 2 of these had been performed at the Mount Sinai Hospital.

There were 8 cases of prolapse of the cervical stump following supracervical hysterectomy for fibroids. In all of these there were, in addition, large cystoceles and rectoceles with almost complete eversion of the vagina.

PREOPERATIVE PREPARATIONS

Patients with extensive cervical erosions or ulcerations of the vaginal mucosa were kept in bed with the cervix and uterus replaced until the ulcerations epithelialized. In a few instances it was found necessary to keep the patients in bed for two weeks before sufficient healing occurred to permit operation. In patients after the menopause, administration of an estrogenic preparation* seemed to promote more rapid healing of the vaginal ulcerations.

Urine concentration tests and phenolsulphonephthalein excretions are done routinely. In the cases of the third-degree prolapse, intravenous urography is performed to determine the status of the kidneys.

In every case a photograph is taken of the prolapse before operation and incorporated in the patient's clinical chart. This makes possible accurate evaluation of the result of the operation when the patient is examined in the follow-up clinic at a later date.

Anesthesia.—Inhalation anesthesia of nitrous oxide and ether was employed with the usual atropine and morphine premedication.

POSTOPERATIVE CARE

The patients are kept on a fluid diet for four days. During the first forty-eight hours $\frac{1}{6}$ gr. of morphine is given whenever necessary. Thereafter mm XX of deod. tinct. of opium is given three times daily.

It is of prime importance to keep the bladder empty. This is accomplished by catheterization every six hours and, if necessary, at shorter intervals. The majority of the patients begin to void after four or five days. At this point catheterization for residual urine should be done. Occasionally patients find it impossible to void for ten and even twelve days. Such patients have no difficulty in voiding as soon as they are out of bed.

On the night of the fourth postoperative day easeara gr. X is given, followed at 6:00 A.M. the next morning by 6 ounces of magnesium citrate. Four hours later the patient is given a soapsuds enema and the packings are removed. The patients are allowed out of bed on the fourteenth day and are discharged usually the next day.

The above technic was employed in 254 ward cases of uterine prolapse. This includes additional follow-up on the 106 cases reported by Frank in 1935.

Complications.—Two of the patients developed secondary hemorrhage from the anterior colporrhaphy suture line, one on the ninth and one on the thirteenth postoperative day. One patient developed a phlebitis of the internal saphenous vein. One patient, six weeks after the operation, developed a pyometria which was drained through the cervix.

Mortality.—There was no mortality in this series.

RESULTS

The importance of frequent follow-up examinations over a period of several years, in order to judge properly the results of a surgical procedure for the cure of prolapse, is self-evident. In this series the patients were examined every three or six months during the first year after the operation, and at six-month intervals thereafter. The period of follow-up observation varied from three months to five years. The routine practice of having a preoperative photograph on every chart is very helpful to the examiner in the follow-up clinic, since it permits of an accurate comparison of the preoperative with the postoperative status.

PERIOD OF FOLLOW-UP	NUMBER OF CASES
4-5 years	12
3-4 years	36
2-3 years	54
1-2 years	76
6-12 months	30
3-6 months	46

In evaluating the results of the parametrial fixation operation, both anatomic and functional criteria were kept in mind.

*We are indebted to the Schering Corporation of Bloomfield, N. J., for Progynon-B employed for this purpose.

Anatomic factors considered were: (1) the presence or absence of descensus of the cervical stump and vault of the vagina with the patient straining in the lithotomy position; (2) descensus of the anterior and posterior vaginal walls.

The functional factors noted were: (1) the presence or absence of a sensation of descensus or of vaginal protrusion; (2) the functional status of the vagina; and (3) general symptomatic result.

As regards the prolapse, the results were surprisingly uniform. With but one exception, the prolapse was cured in the entire series. The findings in these cases, whether one examined them three months or five years after the operation, are strikingly similar. The cervix is usually felt flush with the fornices and on straining there is practically no descent either of the cervix or of the vaginal vault. The most striking results were noted in the cases that had had complete uterine prolapse with large cystoceles and rectocele (and in a few cases also enterocele). The results in this group were as good as in the group of first- and second-degree prolapse.

In the entire series of 254 cases there was one case of recurrence of the prolapse. This was in an asthenic patient aged forty-seven, ten years after the menopause, with a third-degree prolapse and a history of vaginal protrusion of eighteen years' duration. Signs of recurrence were noted three months after the operation. This was the patient who developed a pyometria six months after the operation.

In 15 cases there was considerable sagging of the anterior vaginal wall, but even in these the cervical stump and fornices remained high up on straining. In two of this group there was a recurrence of the cystocele which required a secondary anterior colporrhaphy; one case required a secondary repair for recurrence of the rectocele. One of these cases had required revision of the anterior colporrhaphy because of secondary hemorrhage on the ninth postoperative day which may account for the recurrence of the cystocele.

The parametrial fixation procedure was put to its severest test by the series of cases of recurrent prolapse (following interposition, ventrofixation, etc.) and by the group of 8 cases of prolapse of the cervical stump occurring after supracervical hysterectomy. This group of cases presented complex surgical problems because of the antecedent operations and constituted a genuine challenge to the parametrial fixation operation. The uniformly excellent results in this group, particularly in the two cases of recurrent third-degree prolapse, following unsuccessful interposition operation and in the cases of complete cervical stump prolapse, were very gratifying.

It is interesting to note that not infrequently there was a discrepancy between the anatomic result as viewed objectively by the examiner and the functional result from the patient's point of view. In the majority

of the cases in which sagging of the anterior or posterior vaginal walls was noted the patients had no complaints. Apparently the anatomic criteria employed for perfect anatomic restitutio as estimated with the patient straining in lithotomy were more rigid and theoretical than is required for a good clinical (subjective) result.

In 8 cases the patients complained of dyspareunia. In all but 2 of these the dyspareunia grew progressively less bothersome after the first year. Several of the patients were given graded dilatations with vaginal dilators. In one case the vagina was constricted by a fibrous band which responded to vaginal dilatation. In another in which dyspareunia was caused by a narrowed introitus the condition was corrected by incising the perineum in the midline and resuturing in the opposite direction.

As regards the subjective (functional) results, these were considered very good except in the small group of 8 cases that had dyspareunia, the one case of recurrent prolapse, and the 2 cases with recurrent cystoecles, and the one with recurrent rectocele which required secondary colporrhaphy. Many of the patients volunteered the information that one of the most gratifying results of the operation was the disappearance of vaginal discharge which had apparently originated from the chronically infected, lacerated cervix.

During the course of five years of observation of these cases, one becomes impressed with the fact that as time goes on there is a definite progressive improvement in both the anatomic as well as functional status.

RELATIONSHIP TO PREGNANCY AND PARTURITION

The English schools are of the opinion that the Manchester operation is no contraindication to pregnancy and that labor is not significantly complicated by the operation. It has been the feeling here, however, that pregnancy is preferably to be avoided. Accordingly, the patients who still menstruate are referred for contraceptive instruction. Of late it has become the practice to ligate the fallopian tubes through the vagina in the appropriate cases at the time of the parametrial fixation operation.

In this series 2 patients became pregnant and had uncomplicated labors. One patient was thirty-nine years of age, gravida iii, para ii, had had a second-degree prolapse and became pregnant six months after the parametrial fixation operation. The labor was uneventful. When seen four months after delivery, there was no sign of recurrence of the prolapse. The second patient was thirty-two years of age, gravida xii, para viii, had had a second-degree prolapse and became pregnant fifteen months after the operation. Labor was uncomplicated and when examined four months later, the cervical stump and vaginal walls were found not to descend on straining.

SUMMARY

1. The technic of the parametrial fixation operation is described in detail and the results in a group of 254 cases are reported.

2. This series consists of 126 cases of first-degree prolapse, 85 of second degree, 35 of third degree, and 8 cases of prolapse of the cervical stump occurring after supracervical hysterectomy for fibroids.

3. The operation has the following advantages over other surgical procedures employed for the cure of prolapse, namely:

- a. High percentage of cures.
(there was one case of recurrence in a series of 254 cases; 99.6 per cent cures).
- b. Low morbidity and mortality.
(mortality in this series—0).
- c. The operation is entirely vaginal.
- d. It does not necessitate the removal of the uterus.
- e. The function of the vagina is not compromised.
- f. The operation does not preclude the possibility of subsequent pregnancy and uncomplicated labor.
- g. If necessary, the fallopian tubes can be ligated at the same time, per vaginam.

4. The practice of taking preoperative photographs in every case of prolapse and a thorough follow-up system consisting of examinations at three- to six-month intervals for periods up to five years permitted of precise evaluation of the results of the operation in this series.

5. The procedure has given as good results in cases of complete as in cases of first- and second-degree prolapse.

6. The operation has given excellent results in cases of prolapse of the cervical stump occurring after supracervical hysterectomy.

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100 EAST SEVENTY-FOURTH STREET

Browne, F. J.: *Maternity Services: The Part Played by Education of Medical Students*, Brit. M. J. 2: 384, 1936.

From answers to a questionnaire sent to medical schools in Great Britain and Northern Ireland the author concludes that better obstetric service can be obtained only by better undergraduate and postgraduate training of medical students. He points out channels for improvement in clinical experience and practical ways for the training of undergraduates and the general practitioner.

Clinical instruction should not aim at making the student an obstetric expert. The instructors should be men whose main interest is obstetrics and who give to it their whole time, reside in the hospital and have an adequate staff.

F. L. ADAIR AND S. A. PEARL

GONORRHEA IN THE FEMALE TREATED BY A COMBINED HEATING TECHNIC

WILLIAM BIERMAN, M.D., AND EDWARD A. HOROWITZ, M. D.,
NEW YORK, N. Y.

(From the Department of Physical Therapy, Mount Sinai and Beth Israel Hospitals)

THE fact that the gonococcus is a thermolabile organism which can be destroyed at temperatures tolerable to the human body has led investigators to use various temperature elevating procedures in the effort to destroy this organism within its human host.

Carpenter and his coworkers¹ have reviewed the thermal resistance of numerous strains of the gonococcus. They have found that at 41.5° C. (106.7° F.) these strains will survive heating for different periods varying from six to thirty hours. The upper limit to which the temperature of the entire human body may be raised with reasonable safety is approximately 41.5° C. Continuous exposure of the infected patient to heating procedures sufficient to maintain this systemic temperature for the long periods necessary to exert a thermoethal effect on all of the gonococci in one session is extremely trying both to the patient and to the attending medical staff. We have found that the temperature of the female pelvic organs can be elevated to a considerably higher level (42.8° to 43.3° C. or 109° to 110° F.) for a period of about eight hours. These higher temperatures destroy the gonococci lodged within the pelvic organs in a much shorter period of time than that required at a temperature of 41.5° C. (106.7° F.). In order to maintain these high pelvic temperatures, it is necessary to elevate the temperature of the entire body at the same time.

We have previously described the various technics which we have employed during the past six years.²⁻⁵ The procedure which we now follow is first to elevate the systemic temperature by short wave currents while the patient lies in a cabinet heated by electric lamps (Fig. 1). After the systemic temperature has been elevated to about 41.1° C. (106° F.), we apply the additional local heating to the pelvis, principally by means of diathermy, supplemented for an hour or two by ultrashort wave. At the same time the systemic temperature is maintained at its elevated level.

We use special vaginal electrodes channeled to permit the insertion of a thermometer⁶ (Fig. 2). These electrodes were patterned after casts of the vagina made from living subjects. They are available in four lengths varying from 2¾ inches to 4¼ inches. The electrodes have a relatively large surface area, and no sharp edges, which if present might cause a concentration of current and local overheating of tissue. It is important to use an electrode of proper length in the treatment of each patient, if the urethra as well as the cervix is to be included in the field of high

local temperature elevation. In patients with lacerated perineum, a special electrode support may be necessary to hold the electrode in contact with the urethra.

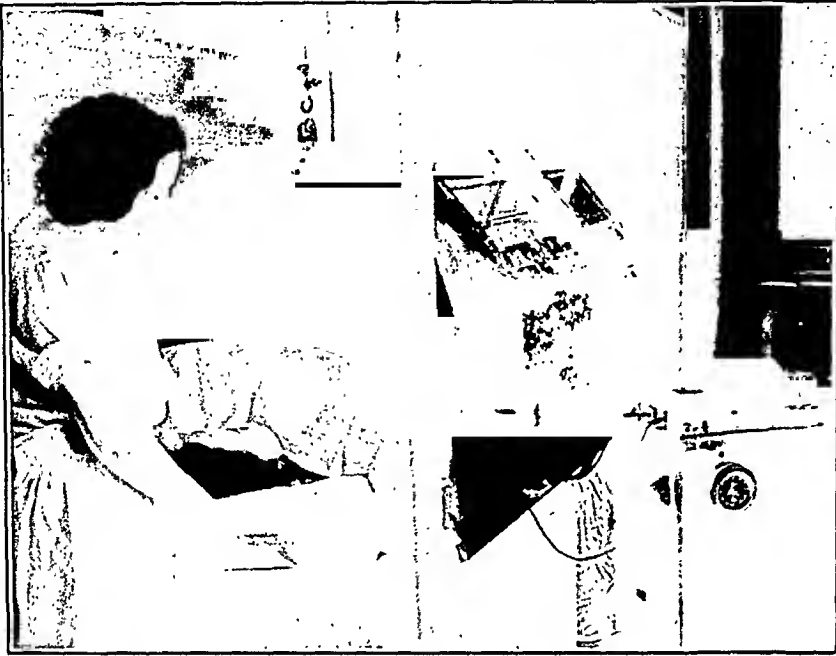


Fig. 1.

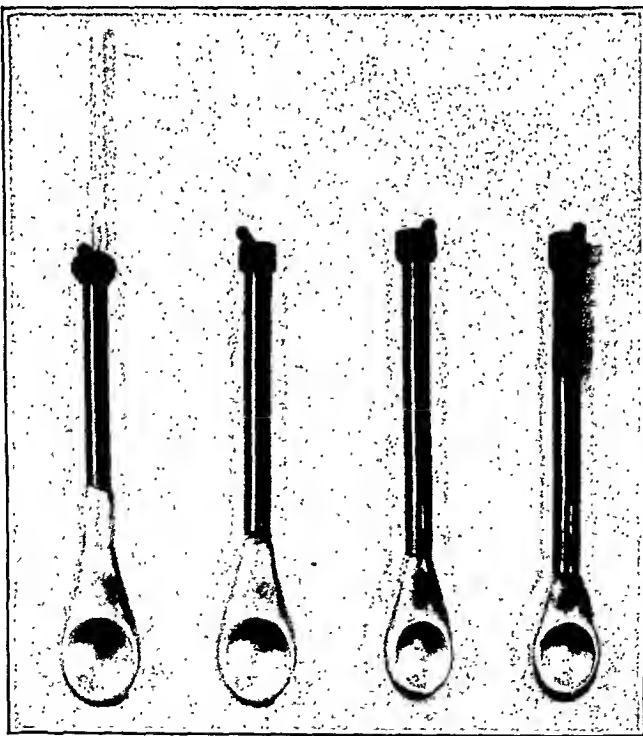


Fig. 2.

The vaginal electrode is connected to one terminal of the diathermy machine. The other terminal is connected to three belt electrodes made of Crooks metal. One belt is placed around the waist, and one around

each thigh just above the knee (Fig. 3). An additional diathermy plate placed in contact with the back has its lower end tucked under the posterior portion of the abdominal belt (Fig. 4). The amount of current required is determined by the temperature reading of the thermometer in the vaginal electrode. Usually it does not exceed 2500 milliamperes, as indicated by the meter on the machine. After three hours, the metal

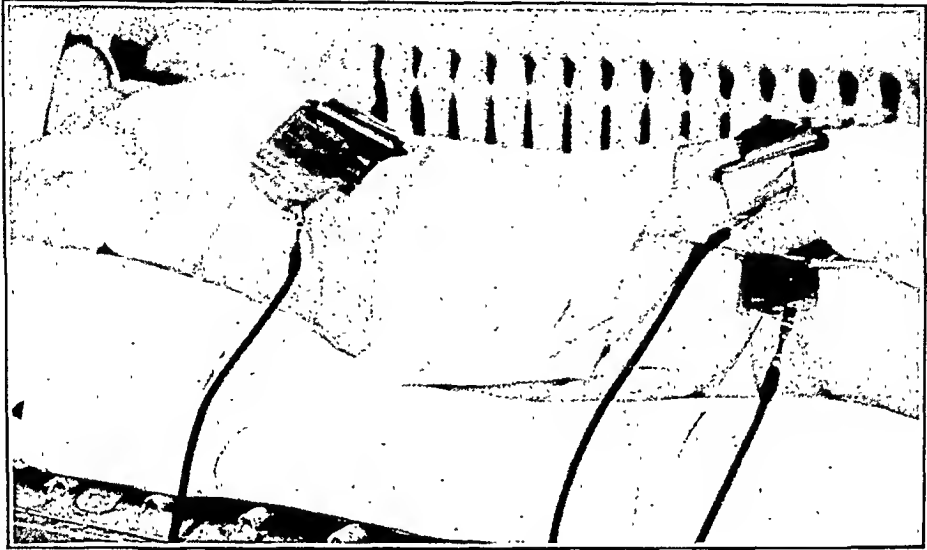


Fig. 3.

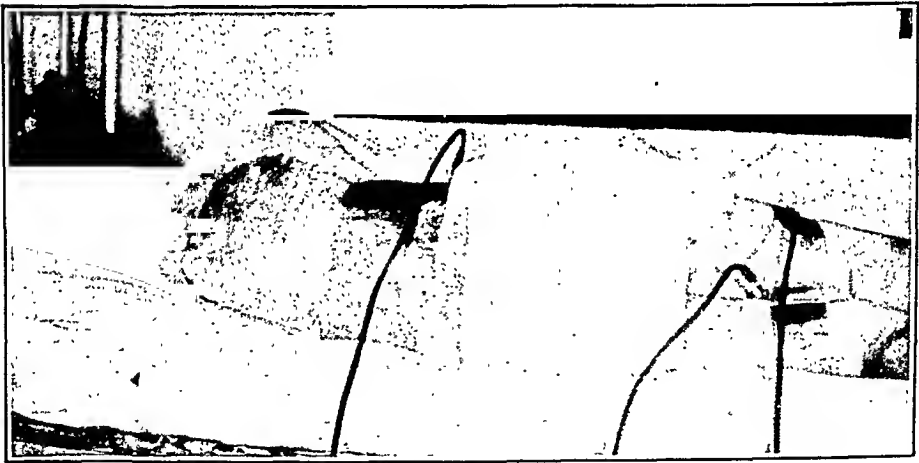


Fig. 4.

belts about the thighs are transferred to the calves of the legs, this arrangement being employed for three or three and one-half hours (Fig. 5). After this, the diathermy belts are all removed.

An additional hour or two of pelvic heating may be given by short wave, using the same vaginal diathermy electrode. The vaginal electrode is connected to the short wave machine by a cable in the course of which a small variable condenser is placed. The condenser plate from the other side of the apparatus may be placed outside the fever cabinet, either

under or over it. This airspacing arrangement is possible only with machines of relatively short wave length. We use an apparatus producing current of six meter wave length.

The multiple dispersive diathermy electrodes are necessary because of the poor tolerance of the subcutaneous fat to prolonged heating by diathermy. With dispersive electrodes which do not have a sufficiently large area of contact, prolonged diathermy treatments may be followed by the formation of painful indurations under the skin covered by the electrodes. The shifting of the diathermy belts at the end of three hours of treatment, from the lower thighs to the calves, was found necessary for the same reason, namely, that with the belts in place about the thighs throughout, induration sometimes occurred under the areas which had been covered by them. Even with the arrangement which we employ,



Fig. 5.

in several cases there have been evidences of overheating of the thighs. This is more likely to occur if the thigh belts have been placed closer to the inguinal region than to the region of the knee. In such cases, on the day following treatment, patients have complained of pain in the inner aspect of each thigh, aggravated by abduction of the thighs. This pain has lasted for only a few days in most cases, but in three instances persisted for a week or two. Upon examination, in addition to the tenderness, we have noted some swelling of the upper inner thigh. This swelling disappears with subsidence of the pain.

The use of short wave currents instead of diathermy in a number of cases throughout the six- or eight-hour period of pelvic heating, was followed by painful thighs and backache in a much higher percentage of those treated, than with our routine diathermic method. We, therefore, consider diathermy our mainstay for pelvic heating, utilizing pelvic

short wave only for a brief supplementary period in some cases. The fact that short wave treatment was followed by painful thighs suggests that heating of the retroperitoneal muscular, vascular, or nervous tissues may be the cause, since the dispersive condenser pad was never in proximity to the thighs.

Patients are encouraged to eat a hearty meal the evening before, but on the morning of the treatment, breakfast consists only of tea and toast or crackers and milk. An enema is given about an hour before the administration of the treatment, which is usually started at about 7 A.M. The lower extremities are wrapped in cotton to avoid skin damage from the heat of the cabinet. We have found that the preliminary hypodermic administration of hyosine and morphine (hyosine hydrobromide gr. $\frac{1}{200}$, morphine sulphate gr. $\frac{1}{6}$) makes the patient more comfortable and also usually facilitates the elevation of temperature because of the interference with sweating. Later, if necessary because of restlessness, additional doses of morphine ($\frac{1}{8}$ gr.) or of hyosine ($\frac{1}{400}$ gr.) may be given at intervals. These sedatives are administered guardedly so as to avoid undue depression of the respiratory center. It is a common experience to observe an elevation of temperature following the administration of a sedative to the hyperthermic patient. If necessary, this is counteracted either by diminishing the amount of heating energy applied to the patient or by increasing heat loss.

The patient is permitted to drink as much as she desires, of either plain water or a 0.6 per cent saline solution. A cold towel placed on the forehead frequently helps to make her more comfortable. As a result of sedation, patients may doze for considerable periods of time.

During the period of pelvic heating by diathermy or short wave, the rectum is also heated additionally. Its temperature, therefore, does not indicate the true systemic level. The systemic temperature is, therefore, determined at intervals of five or ten minutes by means of thermometers placed under the tongue and in the axilla. These temperatures, as a rule, are not permitted to go above 40.8° C. (105.5° F.). We have found it of value in each case, as soon as hyperpyrexia has been produced and before distortion due to pelvic heating occurs, to establish the relationship between the systemic temperature as indicated by the rectal thermometer, and the temperature in the mouth. As a rule, the mouth temperature is about 0.7° F. (0.4° C.) lower than the rectal temperature. However, it may occasionally be 2.0° F. (1.2° C.) lower, and sometimes it may be the same as or slightly higher than the rectal temperature.

Observations must be made not only of the systemic and vaginal temperatures, but also of the patient's general condition, her color, the character and frequency of respiration, and the pulse. A pulse rate beyond 160 beats per minute calls for a lowering of the systemic temperature or the complete cessation of treatment.

The treatment is an uncomfortable one, but there is no pain. There is a definite element of danger if care is not taken to make certain that the systemic temperature does not exceed 41.7°C . (107°F). Continuous watchfulness is necessary. There has been no fatality and no serious complication in any of our cases.

We believe that this treatment is indicated at any stage of gonococcal infection in the otherwise healthy adult female. Patients with organic disease, which would make them poor surgical risks, should not be treated. Pregnant women with gonorrhea should not be treated because of the likelihood of harm to the fetus from the high pelvic temperatures.

Early in our experience a patient was treated during menstruation and developed evidences of salpingitis the next day. Since then, we have refrained from treating any patient during the two days prior to the expected onset of menstruation, during the period, and for two days after the cessation of flow. Other than in the patient just referred to, there has been no instance of extension of the infection in any patient who has received this therapy, even in those cases in which the first treatment did not eradicate all the gonococci.

By means of this combined heating technic, we have treated 121 women, in all of whom the presence of the gonococcus had been determined in either the cervical or the urethral secretion or in both. Of this number, our first series of 67 patients received treatments combining about six hours of systemic fever with about three and one-half to four hours of additional pelvic heating. Of this group, 62 were rendered gonococcus-free in an average of 2.4 treatments per patient. In the five failures the patients received from one to three treatments. Further treatments were not administered for various reasons.

Fifty-four patients were treated in our subsequent series. These patients were subjected to periods of systemic temperature elevation varying from ten to fourteen hours, during six to eight of which additional pelvic heating was administered at a temperature of about 42.8° to 43.3°C . (109° to 110°F). Fifty-one of these patients became gonococcus-free after an average of 1.4 treatments per patient. None of these patients received more than three treatments. Of the three failures in this group, two received one treatment each, after which their smears remained positive. We did not have the opportunity of retreating these two cases. The third patient received four treatments, in spite of which, gram-negative intracellular diplococci could still be demonstrated in smears from the urethra, although the cervix had become negative. We believe that in this instance the organisms were unusually heat-resistant.

The day after treatment, smears are examined and if found still positive, the treatment is repeated on the following day. Once the smears have become negative, examinations are performed each day for several days, then at longer intervals. Treatment is repeated at once if gonococci are again found. Whether a patient will require one, two,

or three treatments depends upon the resistance to heat of the gonococci responsible for her infection, and, to some extent, upon her own resistance to the gonococci. The adequate "heat dosage" in each case is determined by the disappearance of gonococci, and it is only when the gonococci have permanently disappeared that we obtain the therapeutic results to be described.

Within a few days following adequate treatment, there is a subsidence or disappearance of the vaginal discharge. The cervical secretion becomes mucoid and clear, microscopically containing only scattered leucocytes instead of the pus clumps previously found. The urethral smear contains only scattered leucocytes in addition to many epithelial cells and Döderlein bacilli. In a few cases, superficial mucosal burns have caused a prolongation of the discharge. With the healing of the mucosal area within two or three weeks, the discharge disappears. In a few other cases, trichomonas vaginitis has caused a continuation of the discharge following disappearance of gonococci. This discharge ceases with the application of measures aimed against the vaginitis.

About one-third of the cases were complicated by salpingitis. In the acute or subacute salpingitis cases, pain usually disappears during the first treatment. We have observed that treatments may be instituted at any stage of gonococcal infection, even in the presence of acute salpingitis, associated with fever and pelvic peritonitis. Tuboovarian inflammatory masses, including those which are probably suppurative and associated with a rapid sedimentation time, respond satisfactorily to this type of treatment. There is first a diminution or disappearance of pain, and a return of the temperature to normal the day following the treatment. The temperature remains normal. Rapid sedimentation rates become slower.

Pelvic examination within a few days after treatment usually reveals a marked diminution of pelvic tenderness, but little change in the size of the adnexal masses. From seven to ten days after treatment there is usually an increased mobility of the uterus and some shrinkage of the inflammatory masses. After about two weeks following the treatment, the adnexal masses become much smaller.

The first menstrual period following treatment sometimes comes on before the expected time and may be more profuse and of longer duration than usual. We have never observed a cessation of menstruation or the occurrence of menopause symptoms after treatment. A number of patients with chronic salpingitis associated with painful or prolonged menstruation, noticed that menstruation became more normal and less painful following treatment.

Pregnancies and normal delivery have occurred in a number of patients whom we have previously treated for gonorrhea by this technique. In a number of patients with acute salpingitis at the time of treatment, insufflation by the Rubin method has subsequently demonstrated normal tubal patency.

The follow-up on most of these cases has been sufficiently prolonged (in some cases extending for a period of five years) to assure us that the disappearance of the gonococci has been permanent. We have relied upon frequently repeated smears, especially those taken directly after the cessation of menstrual flow. In addition, in many cases we have made cultures. The danger of a woman becoming reinfected by resumption of relations with the sex partner who originally infected her or with some other infected individual is always to be reckoned with. In four cases, after intervals of many months, during which repeated examinations failed to reveal the presence of abnormal discharge or of gonococci, a purulent discharge containing the organisms was again found. In each of these cases, there was a definite history of new exposure to an infected partner.

SUMMARY

We have described a method for the treatment of gonorrhea in women which we have developed and used during the past six years in 121 cases, with success in 113 (93 per cent). The treatment is strenuous, and not without danger. It is a hospital procedure. Adequate apparatus, trained personnel, and continuous watchfulness are necessary. Physically induced fever is combined for six hours with pelvic diathermy, and for two hours with pelvic short wave, so as to produce a vaginal temperature of about 109° to 110° F. (42.8° to 43.3° C.), while the body temperature is held between 105.5° and 106.5° F. (40.8° and 41.4° C.) and continued for a period of about twelve hours. While usually one to three such treatments may be required to eradicate all gonococci, the average number found to be necessary in our last series was 1.4 per patient. The special vaginal and body electrodes and their use are described as is also the care of the patient during treatment. Contraindications, immediate, and late results are discussed.

CONCLUSIONS

The outlook for the woman with gonorrhea has been brightened by the development of the combined heating procedure here described. A rapid eradication of the gonococci can be achieved in most cases, and without danger of extension of the disease. The possible dangers of the heat treatment itself require that it be administered in hospitals, and only by those sufficiently qualified by special training and experience.

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AN ANALYSIS OF 521 CASES OF TWIN PREGNANCY

I. DIFFERENCES IN SINGLE AND DOUBLE OVUM TWINNING

ALAN F. GUTTMACHER, M.D., BALTIMORE, Md.

(From the Department of Obstetrics, Johns Hopkins University)

THE term "twin" in this series of papers shall embrace both the single ovum (monozygotie) and double ovum (dizygotie) varieties. Actually it should be restricted to the one-egg type as it is derived from the Anglo-Saxon, "getwinn," and is related to other words of the same root, such as twaining or two-ing, which imply dividing in two. However, its use to describe two born at the same time has been common English practice since the sixteenth century when understanding of the process was of course very vague.

INCIDENCE OF ALL FORMS OF TWINNING

The 521 cases which form the subject of this study occurred on the combined hospital and home delivery services of The Johns Hopkins Hospital from the inception of its obstetric department in 1896 to Jan. 1, 1937, a period of forty years. During the same period there were 38,496 deliveries of viable children (more than 1,500 gm.) and 2,638 abortions. Among the former were 450 cases of twins, or 1 in every 86.5 viable births, and among the latter 71, or 1 twin abortus in every 37.1 abortions. If the viable pregnancies and abortions be added together and the total cases of twins be divided into this combined figure, we find that one set of twins occurred in every 80 pregnancies.

These figures show striking agreement with those for the whole birth registration area of the United States, where during the five-year period, 1926 to 1930, one pair of twins was recorded to each 86.3 confinements. Since, in the main, abortions are seldom reported, it is likely that the Johns Hopkins figure of 1 twin gestation in every 80 pregnancies would be approximated in the country at large if all abortions were included.

During the same forty-year period there have been 7 triplet pregnancies on the Hopkins Obstetrical Service, 5 of them resulting in children of viable size, a proportion of one set of viable triplets to every 7,699 viable births. The remaining two were abortions, an incidence of one triplet abortus to every 1,319 abortions. If the seven triplet pregnancies be divided into the total pregnancies (viable + abortions) we find an incidence of one triplet pregnancy to each 5,877 gestations.

It is interesting to examine these figures in the light of Zeleny's hypothesis, that if N equals the incidence of twin births in any portion of the

population, the incidence of triplets is N^2 , and quadruplets N^3 . On the basis of the small Hopkins experience, one would expect viable triplets in every 7,482 (86.5^2) viable births, and triplet pregnancies in every 6,400 (80^2) pregnancies. As a matter of fact the figures were 7,699 and 5,877.

THE DIFFERENTIATION OF SINGLE FROM DOUBLE OVUM TWINS

Two methods have been commonly employed to differentiate single from double ovum twins. The first, the study of the twins themselves, and the second, the study of the placental relations.

Those who rely on the first method make the diagnosis by a physical comparison of the members of a pair. Such an investigation is usually best performed between the ages of two and four years, for at this time differences due to inequalities of intrauterine existence have been diminished by the postnatal months and differences created by external environmental factors have not had the opportunity to become marked. To diagnose a pair as derived from one egg, the following physical criteria must be satisfied:

1. Both members of the pair must be of the same sex.
2. Their features, including ears and teeth, must be obviously alike. This resemblance need in no sense be absolute, since in a way each member of such a pair may be thought to represent but one-half of a single zygote and therefore the twins need not resemble each other more closely than the two lateral halves of one individual. The extent of difference or asymmetry between corresponding parts on the opposite sides of a human being may be relatively marked.
3. Their hair must be identical in color, texture, natural curl, and distribution.
4. They must have eyes of the same color and shade.
5. They must have the same skin texture and color, although nevi may be differently apportioned and distributed.
6. They must have hands and feet of the same conformation and approximately the same size.
7. Certain anthropometric values, cephalic index, forearm to upper arm length, etc., must show close agreement in both members of the pair.
8. They must have very similar finger and sole prints. This resemblance may be direct or mirror-imaged. In the former instance the finger prints of the right hand of Twin A must resemble the finger prints of the right hand of Twin B more than finger prints of A's right resemble those of his own left. If the resemblance be mirror-imaged or contralateral then the finger prints of A's right hand must resemble B's left more than they do his own left.

The phenomenon of mirror-imaging in single egg twins is in itself an interesting chapter. The pairs who show it in the configuration of their dermal ridges are likely to show opposite hair whorl, one being clockwise, the other counterclockwise. This mirror imaging may involve deeper structures. In 48 per cent of pairs of single egg twins one member is left handed, the other right handed. Congenital defects and neoplasms are frequently reported mirror-imaged in single egg twins.

Double ovum twins of course show no higher incidence of similarities than any ordinary brothers or sisters at the same age, and left handedness in one member of a pair is no higher than in the population at large (4 per cent).

Many biologists oppose the differentiation of single from double egg twins on the basis of physical similarity or nonsimilarity. They argue that it is fallacious to assume the cause of a thing purely by its result, particularly if the result is sometimes equivocal. They contend that it is very difficult and often impossible to distinguish with assurance those monozygotic twins which are least similar from like-sexed dizygotic twins which bear a very strong sibling resemblance.

The second method of differentiation, that of placental relations, has been used for many years. It is assumed that if the embryos arise from two eggs they either have separate placentas or a fused single placenta with a four-layer partition wall, the amnion and chorion of Twin A in contact with the chorion and amnion of Twin B. This can be determined grossly by peeling apart the four separate layers. Occasionally the two chorions are so adherent that there appear to be but three layers, the fused chorionic membranes sandwiched between the two amnions. On the other hand, if the twins are derived from one egg, only two layers of amnion form the partition wall. Occasionally a double ovum three- or four-layered partition wall may be confused with this two-layered single ovum condition, so that it is safer to check each supposed single ovum specimen by microscopic sections.

In recent years Siemens,¹ Curtius,² Von Vershuer,³ and others have challenged the reliability of the membranes as an absolute criterion of single ovum or double ovum twinning. The first two authorities claim that a four-layered partition wall may in some instances be present in one egg twinning. In such an instance the egg divides when still a young morulla, for example, when it is in the 8 or 12 cell stage. At this early phase no embryo and no Anlage of a placenta is present, the cells are still omnipotential, and when the egg divides two separate placentas and embryos are formed. It is assumed that the usual single egg twinning occurs after the morulla has developed into a blastocyst and that the fission involves only the embryonic area. The blastocyst wall, the primitive chorion which surrounds it, is not involved. Siemens and Curtius compared the physical identity of several pairs of twins many months after birth and found that some obviously identical pairs were reputed to have had even separate placentas at birth.

Von Vershuer reported an instance of the reverse condition, twins who had a single ovum placenta, but whom he considered dizygotic or double ovum on the basis of their physical comparison. He suggests the possibility that the two originally separate chorionic cavities became con-

tinuous owing to the obliteration of the two adjacent chorionic walls which at first separated them. The mechanism for such a phenomenon is difficult to imagine.

In summary then, certain biologists claim that the physical comparison of a pair of twins is the only certain method to discriminate between monozygotic and dizygotic types. On the other hand others assert that the placenta is the most reliable criterion.

EVIDENCES OF A FUNDAMENTAL DIFFERENCE IN THE BIOLOGY OF SINGLE AND DOUBLE OVUM TWINNING

The consideration of the mechanism involved in single ovum and double ovum twinning suggests forcibly that they represent very separate biological phenomena: the one fission of either the morulla or the embryonic area; the other the ovulation and fertilization of two ova within a short space of time. The first process is true twinning or "twaining," the other merely the conception of a litter of two.

In 1934, with this concept in mind, William Walter Greulich,⁴ one of the American authorities in the field of human twinning, investigated the relative importance of heredity in the production of both single and double ovum twins. The type of twin was differentiated solely by the method of physical comparison, the placental relations being unknown. He studied the parental stock of 366 pairs, 93 of which (25.4 per cent) appeared definitely monozygotic. Greulich found that "the parents of monozygotic twins differed from the parents of dizygotic twins in their capacity for twin production: the latter had twins much more frequently than would be expected if twinning were determined by chance alone, while the former showed a frequency of twin births only very slightly higher than the chance expectation." This tendency of excessive twin production by the parents of dizygotic twins was shared by other members of the parents' families: brothers, sisters, parents, aunts, and uncles, while the near relatives of the parents of monozygotic twins showed no such proclivity.

Greulich also analyzed the age distribution of the mothers at the time of the birth of the 273 pairs of dizygotic and the 93 monozygotic twins, and compared each with the frequency curve of the delivery age distribution of six million mothers. He found that the age distribution of the monozygotic producing group was approximately the same as that of the six million, but the dizygotic mothers had an appreciably older age distribution. On the basis of these data he writes: "If monozygotic and dizygotic twinning were merely different expressions of the same twinning tendency, the former manifesting itself more readily in younger mothers than the latter, one would expect the curve of the one to rise proportionally as that of the other falls. Such, however, is not the case, both curves tending more to parallel each other, with each having a dif-

ferent mode. This suggests that monozygotie and dizygotie twinning are phenomena distinct from each other as regards most, or all, of their causative factors."

We thought that it might be valuable to analyze similarly a large series of twin births divided into monozygotie and dizygotie groups on the basis of placental relations and compare the findings with Greulich's. If the results were similar, it would be presumptive evidence that either method, namely, the physical comparison of the twins themselves or their placental relations, is satisfactory for distinguishing between single and double ovum twins.

THE MATERIAL

As we stated previously 521 cases of twins occurred from 1896 to 1937 on the Obstetrical Service of the Johns Hopkins Hospital. In most instances the placenta was carefully described and when any doubt existed as to whether it was a single or a double ovum organ, the partition wall was subjected to microscopic study. Until his death in 1931 most of the specimens were examined by J. W. Williams. For some reason or another the placental examination was not completely trustworthy in 43 cases, so that they had to be excluded from the portion of this study which depends on differentiating single from double ovum specimens. In 478 cases the placental relations were accurately described. Of these 478 cases, 123 were single ovum and 355 double ovum. The proportion found to be monozygotie on the basis of the membranes shows almost embarrassing agreement with the findings of Greulich derived from the physical comparison of twins themselves. Our series showed 25.7 per cent derived from one egg, and Greulich's, 25.4 per cent.

EFFECT OF RACE

The material of The Johns Hopkins clinic is almost equally divided between the black and white races (52.25 per cent black and 47.75 per cent white), so that it seemed unusually well suited for determining whether twinning is more common in one race than the other. There was 56.4 per cent of the twinning in black patients, and since this is only 4 per cent above expectancy, it is likely that the difference is owing to a sampling error and that race is not a significant factor; 57.7 per cent of the dizygotie specimens came from colored patients and 52 per cent from the monozygotie.

RECURRENT TWINNING IN THE MOTHERS OF MONOZYGOTIC AND DIZYGOTIC PAIRS

We thought that some light might be thrown on the biology of the two forms of twinning by determining whether recurrent twinning occurs with equal or different frequency in the two groups. Of the 478 patients, 30 gave the history of having had twins in a previous pregnancy. Of the 30 who gave this history, 28 (93.3 per cent) delivered

double ovum specimens. Fifteen additional patients of the series were delivered of twins in a subsequent pregnancy. Of these, 14 (93.3 per cent) had double ovum specimens at the time of their initial twin delivery. Thus of the 45 cases demonstrating recurrent twinning, 42 were associated with the double ovum variety and only 3 with single ovum twinning.

Unfortunately, our histories did not stress the presence or absence of twinning in near kin, so that we cannot compare the conclusive findings of Greulich in this respect to our own. However, combining his results with ours it seems safe to conclude that double ovum twinning is a definitely inherited specific condition which is likely to recur. Single ovum twinning appears to be a biologic sport which happens by chance and has little tendency to reappear.

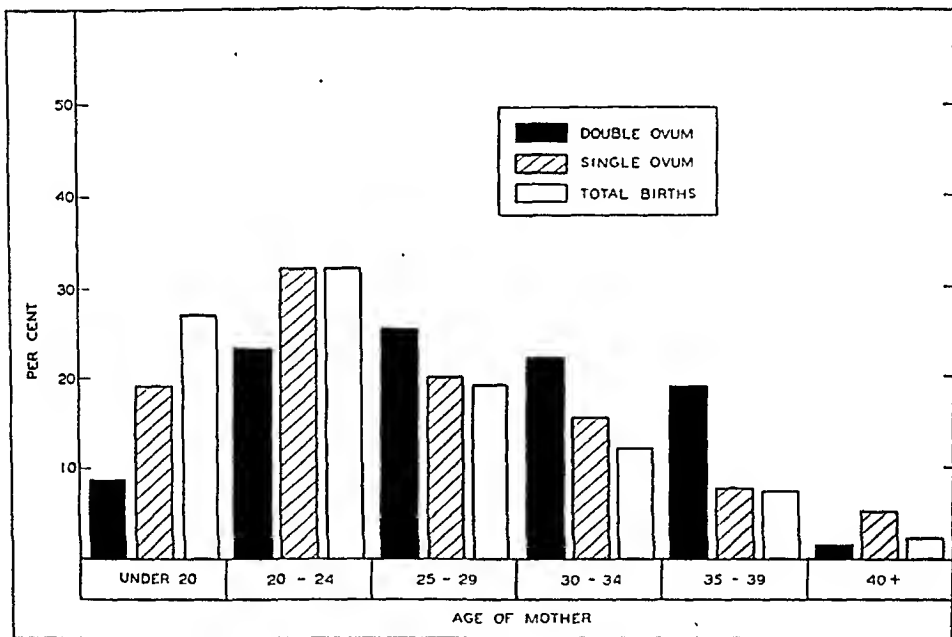


Fig. 1.—473 dizygotic and monozygotic twin-bearing mothers divided into the different age groups and compared with the age distribution of all patients admitted to the obstetrical clinic. For example, the first three columns show that 9.3 per cent of all the dizygotic twins were born to mothers of less than 20 years of age and 18.5 per cent of all the monozygotic, while 27.1 per cent of the total obstetrical clinic population were less than 20 years of age.

AGE OF THE PATIENT

The results of this portion of our survey are recorded in Table I and graphically illustrated in Fig. 1. It seems quite obvious from these data that single ovum twinning occurs with almost the same frequency as the total births for the various age periods. There is a minor tendency to shift from the lowest age group to the older ones. It is significant that by far the most common age group for single ovum twinning is the group (20 to 25) in which the greatest number of total births occurred. On the other hand dizygotic twinning is fundamentally a function of the older age brackets.

In Fig. 2 we have compared our findings for the age frequency of monozygotic and dizygotic twinning with those of Greulich. The structure of his curves and our own are strikingly alike, which proves two things: First, that a real and similar difference has been found in the relation of age to the two forms of twinning by independent observers using different methods on entirely separate material. Second, since these two studies are so similar and since in one case the differentiation into two types was made by the membranes and in the other by a physical

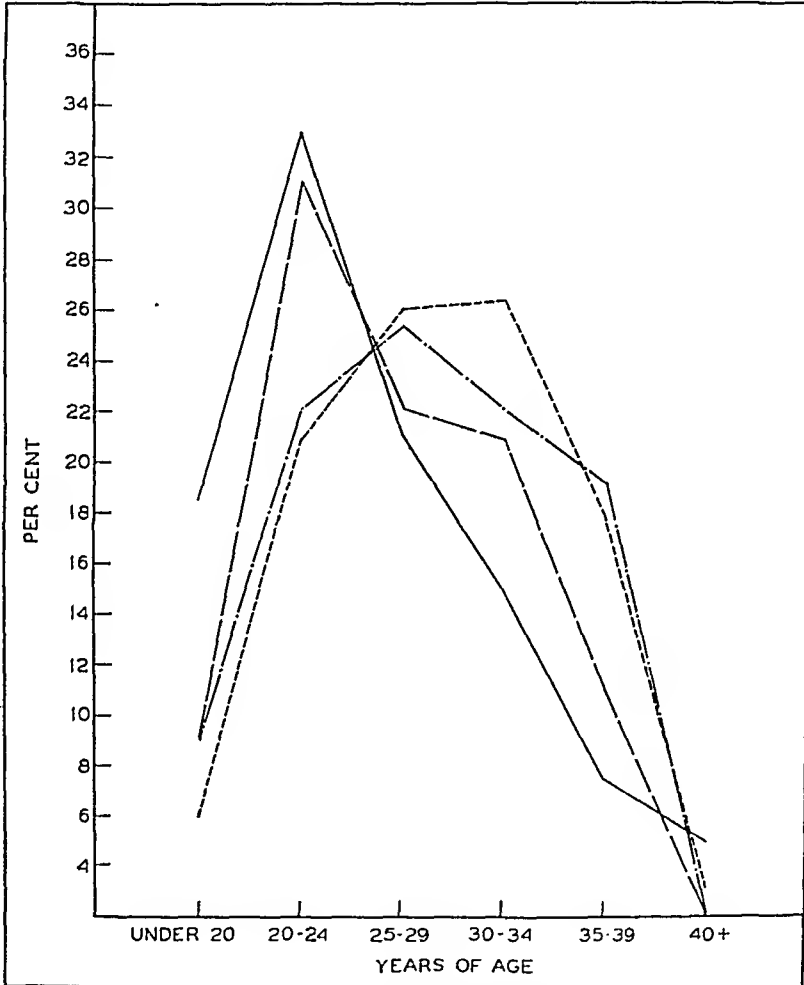


Fig. 2.—Comparison of age distribution of mothers bearing dizygotic twins in two separate series, in one the variety of twin differentiated by a study of the fetal membranes (Guttmacher) and in the other by a physical comparison of the pair years after their birth (Greulich). Note the similarity between the two monozygotic curves and between the two dizygotic curves.

- Age distribution of mothers bearing monozygotic twins as diagnosed by membranes.
- — — — — Age distribution of mothers bearing monozygotic twins as diagnosed by physical resemblance.
- . - . - . — Age distribution of mothers bearing dizygotic twins as diagnosed by membranes.
- - - - - Age distribution of mothers bearing dizygotic twins as diagnosed by physical resemblance.

comparison of the twins years after birth, it may be assumed that either method carefully carried out is satisfactory for separating monozygotic from dizygotic twinning.

PARITY OF THE PATIENT

The influence of parity on the two forms of twinning is recorded in Table II and graphically depicted in Fig. 3. Monozygotic twinning occurs to the women of various parity with the same frequency that would be expected were it just a chance phenomenon. Dizygotic twinning, however, is relatively infrequent in primiparas and secundiparas (two-thirds as frequent as if it were the expression of chance distribution), but it is excessively frequent in the grandes multiparas (twice as common as if it were the expression of chance distribution).

It is impossible to say whether this increased dizygotic twinning in grandes multiparas is just another expression of the age factor or if the

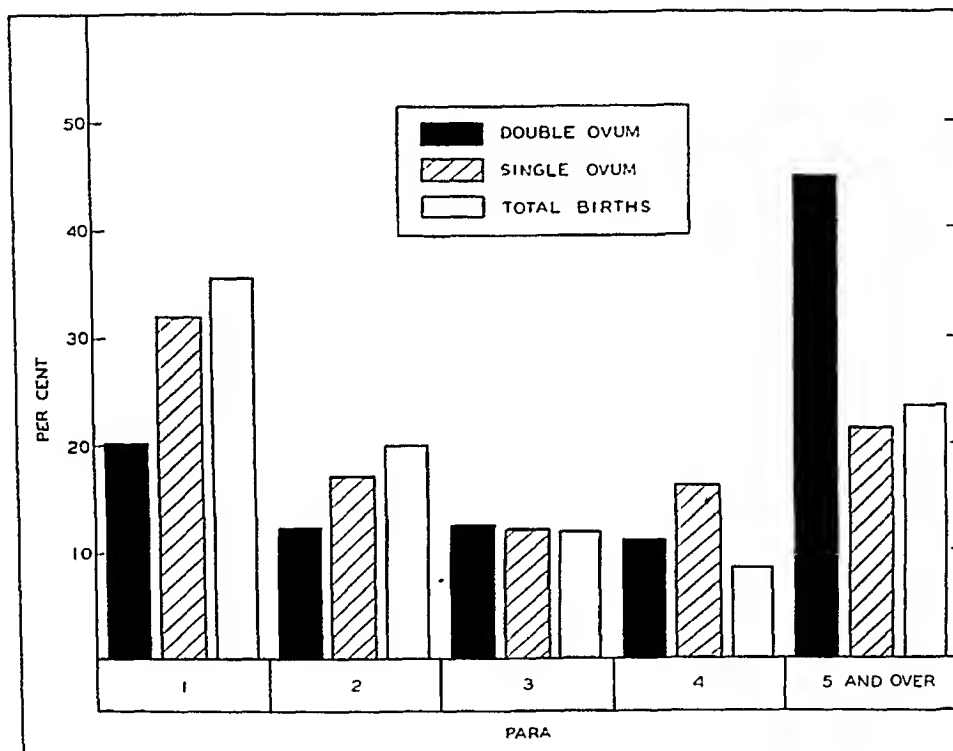


Fig. 3.—476 dizygotic and monozygotic twin-bearing mothers divided into the different parity groups and compared with the parity distribution of the total obstetric clinic population. For example, the first three columns show that 20.2 per cent of all the dizygotic twins were born to primiparas and 31.9 per cent of all the monozygotic, while primiparas formed 35.9 per cent of all mothers who gave birth to viable infants.

TABLE I. THE AGE DISTRIBUTION OF MOTHERS BEARING SINGLE OVUM AND DOUBLE OVUM TWINS COMPARED TO THE AGE DISTRIBUTION OF ALL PATIENTS ADMITTED TO THE OBSTETRICAL SERVICE OF THE JOHNS HOPKINS HOSPITAL

	UNDER 20 YEARS	20-25	25-30	30-35	35-40	40+
General obstetric clinic population, 9,589 con- secutive admissions	27.1%	32.0%	19.1%	11.9%	7.5%	2.4%
Single ovum twins, 119 cases	18.5%	32.8%	21.0%	15.1%	7.6%	5.0%
Double ovum twins 354 cases	9.3%	22.3%	25.4%	22.1%	19.2%	1.7%

TABLE II. THE COMPARISON OF THE PARITY OF MOTHERS BEARING SINGLE OVUM AND DOUBLE OVUM TWINS WITH THE DISTRIBUTION OF PARITY IN THE WHOLE OBSTETRICAL CLINIC POPULATION

	PARA I	PARA II	PARA III	PARA IV	PARA V+
General obstetric clinic population, 29,227 consecutive viable deliveries	35.9%	20.0%	11.9%	8.4%	23.8%
Single ovum twins, 119 cases	31.9%	17.6%	11.8%	16.0%	22.7%
Double ovum twins, 357 cases	20.2%	11.8%	12.6%	10.6%	44.8%

age factor is just another expression of the parity, or if two separate factors are represented. This could only be determined on a series much larger than our own, when the frequency of dizygotic twinning in primiparas of the various age groups could be studied. Also, the frequency of dizygotic twinning in grandes multiparas of the different age levels would have to be investigated.

CONCLUSIONS

1. Monozygotic and dizygotic twinning represent fundamentally separate biologic processes as evidence by differences in heredity, in the likelihood for recurrence and in the influences of age and parity. Monozygotic twinning, true twinning or "twaining," appears to be a chance phenomenon while dizygotic twinning or the birth of a litter of two seems to be regulated by special laws.

2. The differentiation of twins into two types seems to be equally satisfactory if done by a study of the fetal membranes or the physical comparison of the twins themselves months or years after birth.

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Stevens: Congenital Obstructions of the Female Urethra, *J. A. M. A.* 106: 89, 1936.

Diaphragms of valves responsible for symptoms of obstruction are occasionally found in the female urethra. According to Stevens, congenital strictures are also common and meatotomy is the procedure of choice in the treatment of this condition. The olive tip bougie, skenoscope and urethroscope are the most useful instruments for the detection of urethral obstructions. The early detection and correction of obstructing congenital strictures, diaphragms and other conditions are obviously of the greatest importance.

J. P. GREENHILL.

MALIGNANCY OF GRANULOSA CELL TUMORS

WITH A REPORT OF ONE CASE WITH RECURRENCE AFTER SIXTEEN YEARS

BEVERLEY C. COMPTON, M.D., BALTIMORE, MD.

(From the Department of Gynecology, University Hospital)

GRANULOSA cell tumors of the ovary have in recent years appeared frequently in the literature and there are many and varying statements as to their degree of malignancy. These statements vary from that of Dworzak¹ who says, "Clinically the tumors are relatively benign. Recurrence and metastasis are relatively rare," to Novak's figure of a clinical malignancy rate of 28.1 per cent. However, the consensus of opinion is that the malignancy rate is between 5 and 10 per cent. The following table (Table I) will give some idea on this subject, but in view of the fact that some of these figures may overlap due to recent zealous interest in these cases, these are not meant to represent the absolute.

In this series of 187 cases, the outcome of 72 patients has not been recorded. Of the 115 patients remaining, 14 or 12.1 per cent either died postoperatively or the tumor was a postmortem finding, 20, or 17.4 per cent are dead or recorded as inoperable from metastasis or recurrence, and 81 or 70.5 per cent are well from periods varying from two months to fifteen years after operation. Of the latter, Klasten reports one patient living and well eleven years after a second operation, when a tumor identical with that removed at the first operation was removed, and Rummeld reports one case living and well ten years after a second operation.

In view of the interest of these last two cases, I am reporting the following:

A. H., a forty-four-year-old white woman, was admitted to St. Agnes Hospital, Baltimore, on April 17, 1919, with the following history: Married, eight children, all normal deliveries, no miscarriages. The oldest child twenty-four years, youngest eight years. She began to menstruate at eleven years of age and the periods had always been regular and normal. She had enjoyed perfect health until nine months before, when she began to have some pain in the right iliac region, and about one month later she noticed a lump in this region which felt about the size of a hen's egg. This gradually enlarged and with increase in size the pain increased in intensity.

Examination showed the liver and spleen not palpable. She was not sensitive to pressure in the region of their location. A large tumor was easily palpable in the lower part of the abdominal cavity which it seemed to fill and extended upward to the umbilicus. On palpation it seemed to be hard and firm on the right side and rather soft on the left. There seemed to be two tumors, the right feeling like a fibroid, the left like an ovarian cyst. The urine was negative.

On April 22, 1919, through a midline suprapubic incision, J. K. B. E. Seegar disclosed a large, irregular, ovarian mass with a distinct sulcus pushing it in the midline. One-half of the tumor was very soft and filled with bloody fluid, the

TABLE I

AUTHOR	NO. OF CASES	POSTOPERATIVE DEATHS OR POSTMORTEM FINDING	DEATH OR HOPELESS CASES FROM METASTASIS OR RECURRENCE	WELL	OUT-COME UNACCOUNTED
Aschner ²	2		1 died with recurrence 6 mo. after operation	1 living and well 1½ yr. after operation	
Brenner	3	2 found at postmortem exam. 1 died after operation			
Compton	1			1 living and well 1 yr. after second operation and 17 yr. after first operation	
Dailey ³	2				2
Dworzak ¹	1			1 living and well 1½ yr. after operation	
Eastlake ⁴	1(?)			1 living and well 2 yr. after operation	
Elterich ⁵	1	No operation			1
Fahmy ⁶	3				3
Frankl ⁷	1				1
Gottschalk	1			1 living and well 4½ yr. after operation	
Habbes ⁸	32	2	1 died one yr. after operation and 17 yr. after first operation	8 living and well under 1 yr. 3 living and well under 2 yr. 4 living and well 4 yr. 1 living and well 5 yr. 1 living and well 10 yr.	12
Holmer ⁹	1		1 recurrence in less than 1 yr. Outcome not reported		
Isbruch ¹⁰	3			1 living and well 11 yr. after operation 2 lived for many yr. in perfect health	
V. Kahliden	1				1
Kelley and Gnassi ¹¹	1				1
King ¹²	2				2
Klaften ¹³	10	1 died of pneumonia after operation 1 died, carcinoma of stomach		7 living and well 1 living and well after removal of 11 yr. recurrence	
Krompecher ¹⁴	13				13
Lepper, Baker and Vaux ¹⁵	7			6 living and well 4 to 15 yr. after operation 1 living and well 11 mo. after operation	

TABLE I—CONT'D

AUTHOR	NO. OF CASES	POSTOPERATIVE DEATHS OR POSTMORTEM FINDING	DEATH OR HOPELESS CASES FROM METASTASIS OR RECURRENCE	WELL	OUT-COME UNACCOUNTED
R. Meyer ¹⁶	33	1	3	19 living and well 1 to 4 yr. after operation	10
Mullerheim	2			1 living and well 8 yr. after operation	1
Murphy ¹⁷	7	1 died 9 yr. after operation with cerebral hemorrhage 1 died 6 days after operation	1 died 13 mo. after operation 1 died 6 mo. after operation	1 living and well 3 yr. after operation 2 living and well 1½ yr. after operation	
Neumann ¹⁸	6	1	1 died in 6 mo. with recurrence	4 living and well 2½ yr. after operation	
Novak ^{19, 20}	30	2	4 (inoperable) 1 recurrence in 3 yr. 1 recurrence in 1½ yr. 1 recurrence in 7 yr. 1 recurrence in 1½ yr. 1 recurrence in 2½ mo.	1 living and well 2 mo. after operation 1 living and well 1 yr. after operation 1 living and well 2 yr. after operation	16
Plate ²¹	1				1
Robinson ²²	1				1
Rummeld	1			1 living and well 10 yr. after second operation	
Scheyer ²³	1				1
Schiffmann ²⁴	2 1(?)				2 1
Schroder	1				1
Schulze ²⁵	4		1 died 4 yr. after operation with recurrence	2 living and well 1 yr. after operation 1 living and well 11 mo. 1 living and well 15 yr.	
Soltmann ²⁶	1	1 died 10 days after operation	Spinal metastasis found at postmortem		
Taylor ²⁷	1			1 living and well 3 yr. after operation	
TeLinde ²⁸	4			1 living and well 4 yr. after operation 2 living and well 2 yr. after operation 1 living and well 1 yr. after operation	
Taussig ²⁹	1				1
Tietze ³⁰	1				1
Voigt	1		1 died in 6 mo. with recurrence		

TABLE I—CONT'D

AUTHOR	NO. OF CASES	POSTOPERATIVE DEATHS OR POSTMORTEM FINDING	DEATH OR HOPELESS CASES FROM METASTASIS OR RECURRENCE	WELL	OUT-COME UNACCOUNTED
Wolfe and Kamins-ter ³¹	2			1 living and well 6 mo. after operation 1 living and well 15 yr.	
Total	187	14 (7.5%)	20 (10.6%)	81 (43.3%)	72 (38.6%)
% of 115 cases followed		12.1	17.4	70.5	

other very hard and glandular (?). This gave the physical appearance of a bilateral cyst, especially as the soft one occupied the left side of the abdomen and the hard one the right side. There were numerous adhesions to the bladder and posterior surface of the broad ligament and to the omentum and small intestine, the most serious being to the mesentery of the lower ileum. In trying to lift the tumor through the incision the right tumor ruptured and some fibrin and serous fluid escaped into the general peritoneal cavity. Later the two halves of the cyst, where it was connected by a very narrow isthmus about 3 cm. wide, parted. It was very friable and broke with very little tension. The pedicle was elongated, and it was ligated very low down on the broad ligament, and the tumor along with the left tube was removed. The right tube and ovary were normal in appearance. The uterus was very much enlarged to about the size of a two months' pregnancy and was very soft. The appendix was not examined.

Following this, a pathologic examination was made by the late Dr. J. C. Bloodgood which described the two tumors separately as measuring "16 by 12 by 7 cm." and "18 by 8 by 4 cm." and both as having "a distinct capsule" and being "generally cystic" with the cysts containing "clear, blood-stained, and bloody fluid." "The tissue beneath and beyond the capsule" was described as looking "like the cortex of the brain" and was "soft and breaks like brain tissue demonstrating little or no intracellular stroma."

The microscopic picture was described as "a carcinoma, cells occurring in large lobes with only a very fine stroma, and in smaller strands with more stroma." The cells have moderately well-stained protoplasm and round or oval reticulated light, to dark, staining nuclei. Mitoses seen. Also areas of same tumor invading fibrous tissue, some hemorrhage, and necrosis in some places almost resembling caseation.

Following this operation, convalescence was uneventful, and the patient was not seen until sixteen years later when she came to me at the Hospital for the Women of Maryland, Baltimore, on June 11, 1935, at the age of sixty, complaining of a tumor of the womb. At this time she stated that four years before she had started to bleed vaginally for the first time since the above operation. This bleeding was small in amount and lasted four days. It then stopped until two years before, since which time she had had occasional bleeding and for three weeks a small amount each day.

On June 16, 1935, she was admitted to the hospital (Unit No. 9066). Besides the above history of bleeding and her previous history, she only added that she had a slight urinary frequency and occasional nocturia. She had also noticed for a few months that her "stomach would get very large and hard at times." Examination showed a lower midline abdominal palpable mass which was not tender and seemed to be on the anterior uterine wall.

On June 19, 1935, through a suprapubic midline incision, the omentum was found to be markedly adherent to the old scar and left adnexal region, and there was some old free blood in the peritoneal cavity. The adhesions were freed, revealing a mass about 10 cm. in diameter in the right vesicouterine fold which felt cystic in areas, under smooth peritoneum, but apparently on top of and not involving the bladder. The left tube and ovary had been removed at previous operation and the uterus, which was pushed posteriorly, was soft and about the size of a one and one-half months' pregnancy. The right tube and ovary were free and normal and in no way connected with the mass in the right vesicouterine fold. This mass was first dissected free by splitting the peritoneum and freeing it from the bladder and anterior uterine wall to which it was adherent. A routine supravaginal subtotal hysterectomy and right salpingo-oophorectomy was then done, the appendix and gallbladder examined and found to be entirely normal, and the abdomen closed following which a posterior colporrhaphy was done. Her convalescence was uneventful.

Pathologic Report.—*Gross:* 1. A globular mass of tissue measuring 8 cm. in diameter, nodular, soft in consistency, resembling a cyst, completely encapsulated with a thin-walled capsule and a bluish mottled color. On section the capsule was

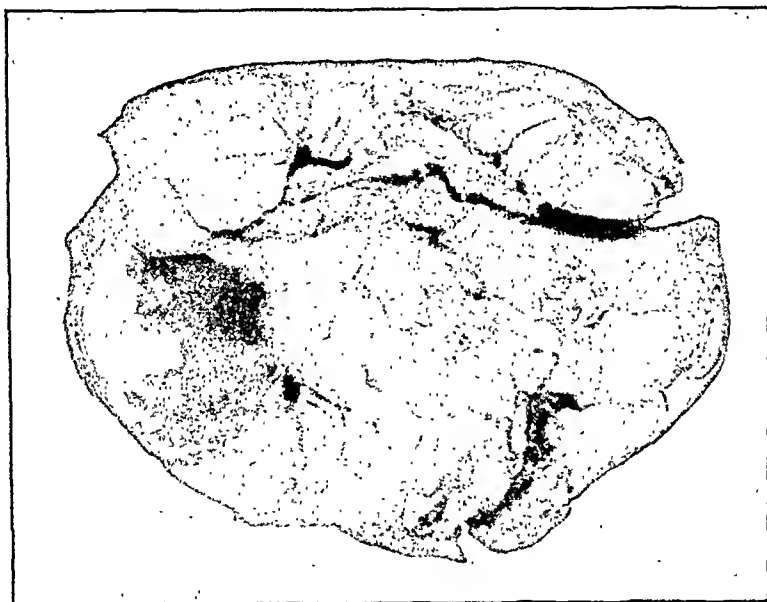


Fig. 1.—Tumor bisected showing continuity of capsule, hemorrhagic areas, and areas of necrosis.

rough in appearance, giving the impression that it was adherent to adjacent structures. On section there were several hemorrhagic cystic areas, the largest $1\frac{1}{2}$ cm. in diameter. The substance cut with ease and was of a light color, aptly described as "like cooked sweetbreads." One area had a necrotic appearance (see Fig. 1).

2. *Uterus:* Supracervically removed and previously opened measuring 11 by 8 by $5\frac{1}{2}$ cm. Walls were $3\frac{1}{2}$ cm. thick. The cavity appeared slightly enlarged and the endometrium was thickened and had a hyperplastic appearance (Fig. 2). The right tube and ovary were attached and the tube was 7 cm. long and normal in appearance with the lumen patent and fimbria open. The ovary was normal in size and appearance.

Microscopic: 1. *The mass:* There were some areas of masses of regular, round, somewhat clear cells tending to group in cylinders and pseudoalveoli whereas in other areas these cells were arranged about blood space (see Figs. 4, 6, and 8).

2. *Uterus:* The uterine wall was normal but thick and the endometrium was surprisingly thick for a patient of this age with the glands greatly distorted in size and showing typical hyperplasia. The tube was normal and the ovary showed only marked senile atrophy (see Fig. 2).



Fig. 2.—Typical Swiss-cheese pattern of endometrial hyperplasia.

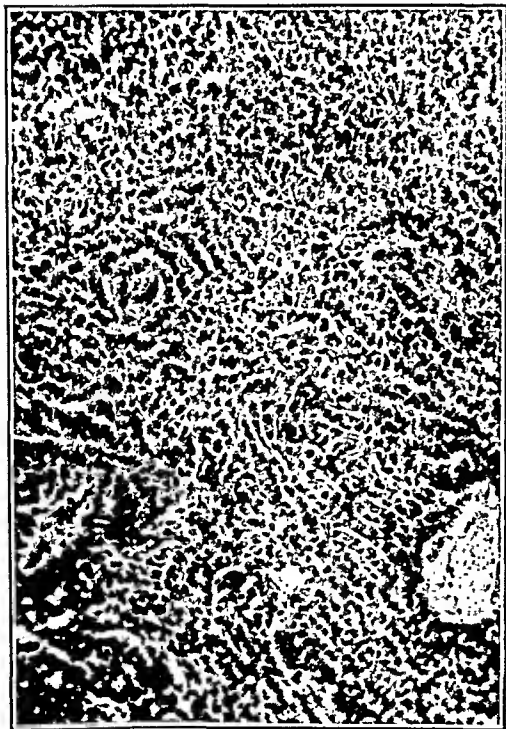


Fig. 3.

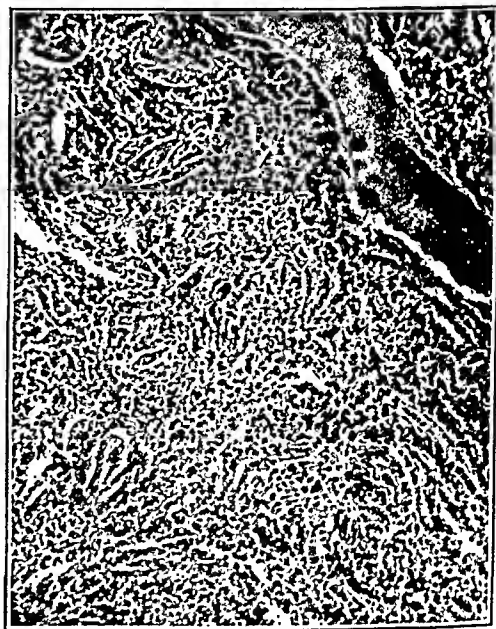


Fig. 4.

Fig. 3.—Photomicrograph of original tumor showing cylindromatous type with multiple mitotic cells.

Fig. 4.—Photomicrograph of recurrence, slightly lower power than Fig. 3, showing cylindromatous pattern.

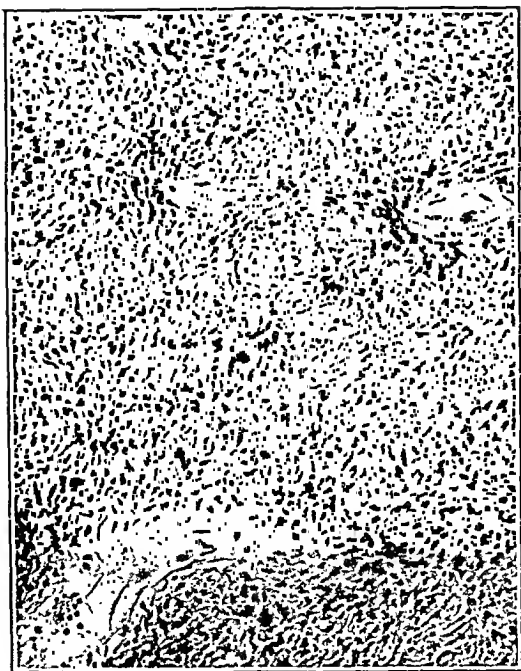


Fig. 5.

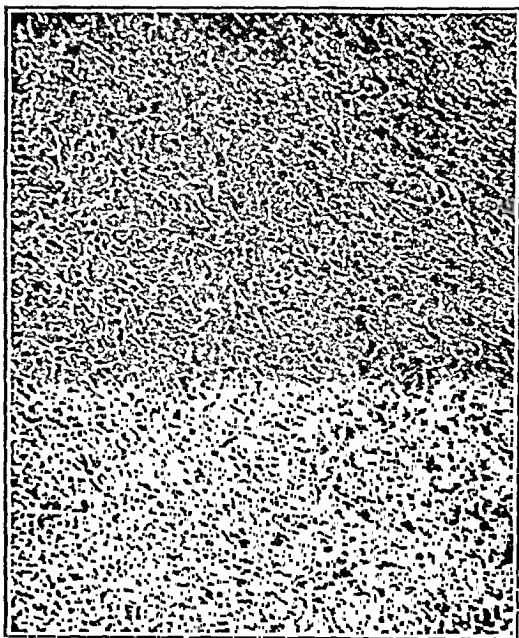


Fig. 6.

Fig. 5.—Photomicrograph of original tumor showing area of fibrosis and cells in strandlike pattern.

Fig. 6.—Photomicrograph of recurrence showing cells in strandlike pattern.

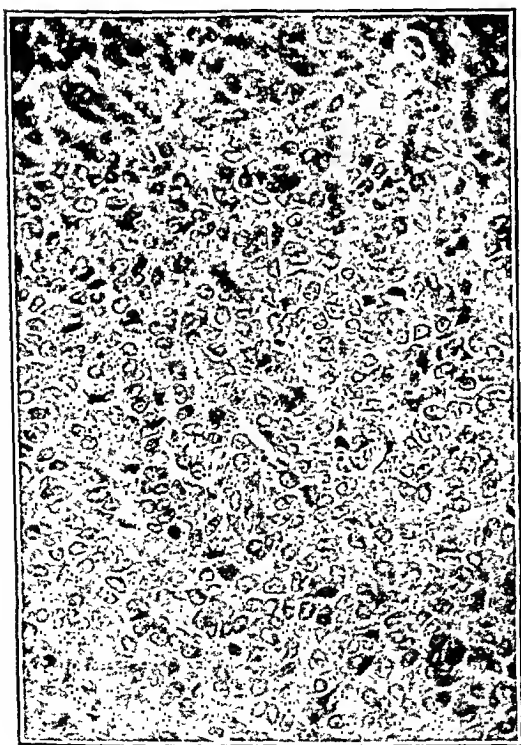


Fig. 7.

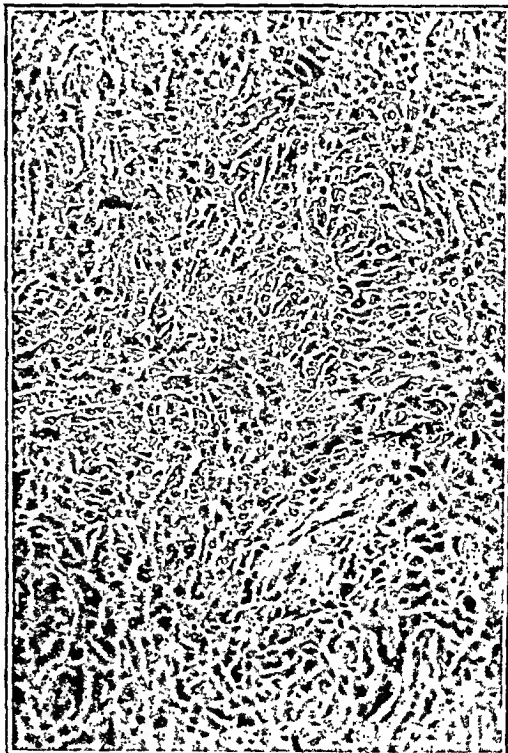


Fig. 8.

Fig. 7.—Photomicrograph (higher power) of original tumor in very cellular area.

Fig. 8.—Photomicrograph (higher power) of recurrence showing mitotic figures, cylindromatous arrangement, and some fibrosis.

The sections of the tumor were at a later date seen by J. M. Hundley, Spencer, Novak, and myself of Baltimore and by George Stewart of New York and Robert Meyer of Berlin and the diagnosis of granulosa cell tumor was made.

The sections of the tumor removed in 1919 were then procured through George A. Stewart of the Johns Hopkins Hospital and photomicrographs were made which are here shown comparing them with the tumor removed June 19, 1935. The tumor removed in 1919 is shown in Figs. 3, 5, and 7; the recurrence in Figs. 4, 6, and 8.

It is seen that these two tumors are identical in appearance, there being no microscopic differences except in the intensity of the stains, but the first tumor definitely arose from the left ovary whereas the recent tumor had no connection with the remaining right ovary but arose in the vesicouterine fold. Furthermore, the latter was beneath glistening healthy peritoneum which showed no evidence of adhesions or other abnormalities. Thus, I am led to assume that the recurrence arose either from aberrant ovarian tissue with a granulosa cell rest or from a transplant of the previously removed tumor.

In September, 1936, fourteen months after the second operation, this patient was seen and examined. The operative result was good and no evidence of recurrence could be found. X-ray therapy was advised for the second time and refused.

In this case which I have presented, the patient at forty-four years showed a large left ovarian neoplasm with an enlarged somewhat boggy uterus, but no menstrual irregularities or intermenstrual bleeding. Sixteen years later, some years after the expected menopause, she again showed an enlarged uterus with definite endometrial hyperplasia, a pelvic neoplasm microscopically identical with the first tumor, and periodic uterine bleeding. These findings all show evidence of excessive and prolonged folliculin stimulation produced by this feminizing type of tumor.

Whether the second tumor arose from a granulosa cell rest or from a recurrence of the previously removed tumor, I cannot say or prove, but the evidence leads me to lean toward the former.

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TREATMENT OF OBSTRUCTED FALLOPIAN TUBES IN STERILITY BY DIATHERMY AND TUBAL INSUFFLATION

MAURICE E. MINTZ, M.D., F.A.C.S., NEW YORK, N. Y.

SURGICAL reestablishment of the lumen of the fallopian tubes has met with only limited success. It is most successful when the obstruction is at the fimbriated end of the tube. When the obstruction is at the isthmie or intramural portion, the results from surgical correction have proved less satisfactory. Any nonsurgical measure which has some promise of improving the tubal status must be considered worth while. Repeated insufflation has in a number of instances proved to be effective.

I have found that diathermy treatment combined with insufflation exerts a reparative influence on some chronically diseased tubes, leading to the restoration of patency, and is followed by pregnancy in many instances.

The beneficial effects of diathermy are produced by the action of heat. The heat is generated by a high frequency current passing through the tissues between two metal electrodes, the greatest concentration of heat being near the smaller electrode. The essential therapeutic action of heat produced by diathermy is said to be due to two factors: (1) An increase in the volume of blood flow to the area treated, due to vascular dilatation; (2) A rise in local metabolism, the degree of which depends upon the actual temperature attained. Relief of pain and of spasm usually results. The explanation of this effect, however, is not yet clear. The increased permeation with heated blood is probably the therapeutic factor of most importance. Diathermy distributes the heat deeply in the tissues, rendering the vascular dilatation widespread and therefore more effective than methods of superficial heat application.

This report is based on the treatment of 44 cases of tubal obstruction as determined by tubal insufflation before treatment was started. There were 30 cases of primary sterility and 14 cases of secondary sterility. Of the 44 patients treated, patency was reestablished to some degree in 25 cases. Of these 25 women, 9 became pregnant and gave birth to normal children. Two patients developed ectopic pregnancies necessitating operation. In 14 instances no pregnancies have been noted as yet.

Each patient received diathermy treatments one to three times a week, total ranging from 15 to 59 treatments. Each treatment lasted

from thirty to forty-five minutes, using from 2,500 to 3,000 milliamperes of current with the abdominal and sacral electrodes. When the abdominal and vaginal electrodes were used, the current employed was only 2,000 to 2,500 milliamperes. The electrodes used were a concave vaginal electrode, and for the abdomen and sacrum, ordinary Cook's malleable tin metal, five by eight inches long, twenty-two gauge, made by Westinghouse Electric Company.

TECHNIC

Abdominal-Vaginal.—1. The patient is placed upon an ordinary wooden table and draped as for a gynecologic examination. An anterior plate, five by eight inches, is placed over the abdomen just above the symphysis and the same size plate placed posteriorly. Both are connected to one pole of the diathermy apparatus.

2. A lubricated concave vaginal electrode is then inserted into the posterior vaginal fornix underneath the cervix, the concavity of the electrode facing anteriorly and connected to the other pole of the diathermy apparatus.

3. The current is then gradually increased so that the maximum amount, 2,500 milliamperes, is reached in about ten to fifteen minutes and this is maintained throughout the treatment.

Abdominal-Sacral.—In the abdominal-sacral method, the same size plates are used but the anterior plate is connected to one pole of the diathermy apparatus and the sacral plate to the other pole. The current is raised to 3,000 milliamperes.

4. Until patency is established, the patient receives two tubal insufflations a month, each immediately following the diathermy treatment. The pressure is kept at 200 mm. of mercury at first for fifteen seconds, then thirty seconds, and finally as long as sixty seconds, depending upon the degree of pain and discomfort it causes. After patency is established the patient receives one tubal insufflation a month, one week after the menstrual period, immediately following the diathermy treatment, until normal tubal contractions are obtained or approximated.

The number of diathermy treatments in the 14 patients in whom tubal patency was reestablished but who did not become pregnant is shown below:

1 patient	10-20 treatments
1 patient	20-30 treatments
8 patients	30-40 treatments
3 patients	40-50 treatments
1 patient	50-60 treatments

The average number of diathermy treatments per patient was thirty-five, and the average time to establish patency was seventeen weeks.

The number of diathermy treatments in the 9 patients who became pregnant were as follows:

1 patient	20-30 treatments
5 patients	30-40 treatments
2 patients	40-50 treatments
1 patient	50-60 treatments

The average number of diathermy treatments per patient was thirty-eight. The average time necessary to establish patency was sixteen weeks.

Two cases (1 and 2) illustrating the tubal status before, during, and at completion of treatment of two patients who did not become pregnant are given here.

CASE 1.—G. H., aged twenty-six, married four years, was never pregnant. Her menses began at the age of twelve, every twenty-eight days, of four days' duration, moderate in amount. There was no pain except slight backache the first day of each period. Patient had a tonsillectomy nine years ago followed by pneumonia. No contraceptives were ever used. Hühner test positive.

Vaginal examination showed a normal introitus. The cervix was normal. The uterus was of moderate size, anteflexed, not freely movable. Both adnexa were enlarged, thickened, but not tender. Smears for gonococci were negative. This patient gave a history of pelvic gonorrheal infection ten years ago.

This patient received five tubal insufflations and 33 diathermy treatments before patency was reestablished (see Figs. 1, 2, 3, 4, and 5).

CASE 2.—H. S., aged twenty-seven, married seven years, never pregnant. Condom contraception was practiced for the first two years. Menses began at the age of sixteen, every thirty days, of five days' duration with moderate bleeding. Cramps occurred on the first day of each period.

Vaginal examination showed a normal introitus. Cervix was normal. Small anteflexed uterus, freely movable. Both adnexa were enlarged and thickened but not tender. Patient gave a history of neisserian infection ten years ago. Smears for gonococci were negative. Hühner test was positive.

This patient received five tubal insufflations and 39 diathermy treatments before normal patency was reestablished (see Figs. 6, 7, 8, 9, and 10).

I am presenting here two cases (3 and 4) illustrating the tubal status before, during and at the completion of treatment of two patients that developed ectopic pregnancies.

CASE 3.—M. B., aged thirty, married eight years, never became pregnant. Appendectomy with drainage six years ago. Dilatation and curettage for sterility three years ago. Menses began at the age of fourteen, every twenty-eight days, of four days' duration with moderate flow. Severe backache the first two days of each period.

Vaginal examination showed a moderate sized uterus, retroverted but movable. Right adnexa was normal. The left was enlarged and thickened but not tender. Smears for gonococci were negative. Hühner test was positive.

This patient had five tubal insufflations and 43 diathermy treatments and became pregnant two months after the last tubal insufflation, developing a right ectopic pregnancy requiring operation. This patient gave birth to a normal child two years later (see Figs. 11, 12, 13, 14, and 15).

CASE 4.—M. D., aged twenty-three years, married five years. Had one child four years ago, instrumental delivery, followed by a mild postpartum sepsis. Menses began at the age of fourteen, every three or four months, lasting five days, with very little flow. Hühner test was positive.

Vaginal examination showed a retroverted uterus, not freely movable. Both adnexa were enlarged but not tender. Smears for gonococci were negative.

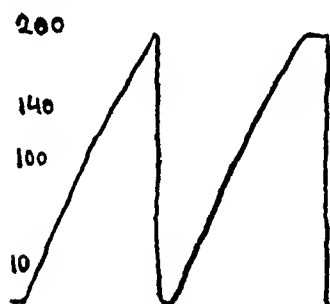


Fig. 1.

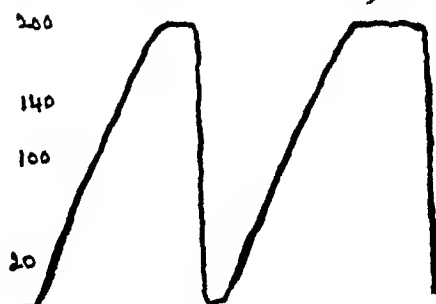


Fig. 2.

Fig. 1.—Case 1. First Rubin Test: The pressure rose to 200 mm. of mercury the first time, then was allowed to drop. The second time the pressure rose again to 200 mm. and was kept there for half a minute. The patient had central abdominal pain during the test; there were no shoulder pains when sitting up.

Fig. 2.—Case 1. Second Rubin Test: The pressure rose to 200 mm. of mercury and was maintained for half a minute the first time. The second time the pressure was kept at 200 mm. for almost one minute. The patient experienced slight central abdominal pain during the test; but no shoulder pain when sitting up.

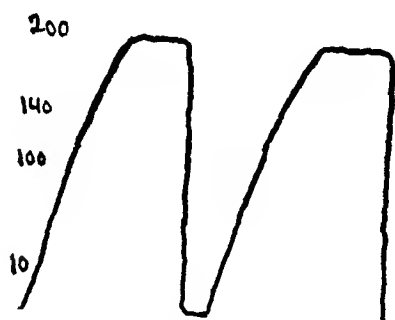


Fig. 3.

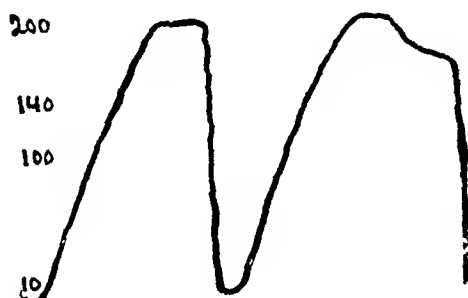


Fig. 4.

Fig. 3.—Case 1. Third Rubin Test: After ten diathermy treatments the pressure twice rose to 200 mm. of mercury; the first time the pressure was held for half a minute, and the second time for three-quarters of a minute. Very little pain was experienced during the test; shoulder pain was noted when sitting up.

Fig. 4.—Case 1. Fourth Rubin Test: After twenty-one diathermy treatments the pressure rose to 200 mm. of mercury and was kept there for half a minute, then allowed to drop. The second time the pressure rose again to 200 mm. and gradually dropped to 160 mm. No shoulder pain was complained of when sitting up.



Fig. 5.—Case 1. Fifth Rubin Test: After thirty-three diathermy treatments the pressure rose to 180 mm. of mercury. The patient experienced severe pain in the right lower quadrant during the test. The pressure gradually dropped to 130 mm. and fluctuated around 130 mm. with very little tubal contractions. The patient had severe pain in the right shoulder four hours after the test.

This patient had 3 tubal insufflations and 24 diathermy treatments and developed a left ectopic pregnancy four months after the last tubal insufflation (see Figs. 16, 17, and 18).

Two cases (5 and 6) illustrating the tubal status before, during, and at the completion of treatment of two patients that developed normal pregnancies are given here.

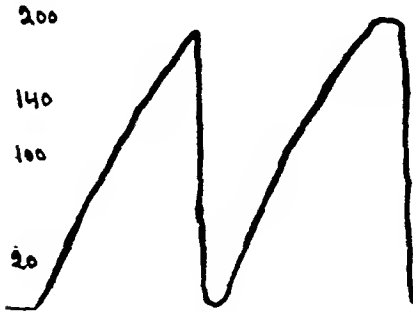


Fig. 6.

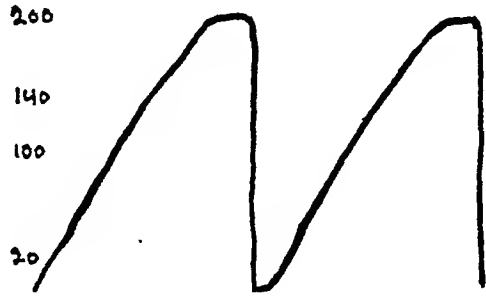


Fig. 7.

Fig. 6.—Case 2. First Rubin Test: The pressure rose twice to 200 mm. of mercury; the second time the pressure was kept at 200 mm. for half a minute. Slight central abdominal pain occurred during the test, also pain in the left lower quadrant. No shoulder pain was complained of when the patient sat up.

Fig. 7.—Case 2. Second Rubin Test: After twelve diathermy treatments, the pressure rose to 200 mm. of mercury and was maintained at that level twice for half a minute. The patient complained of pain in the left lower quadrant during the test; but no shoulder pains when sitting up.

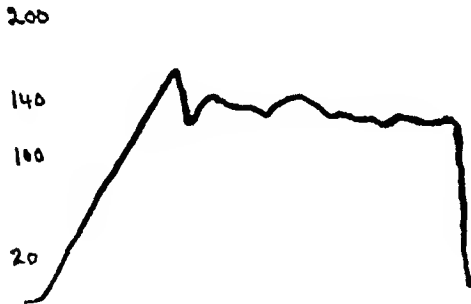


Fig. 8.

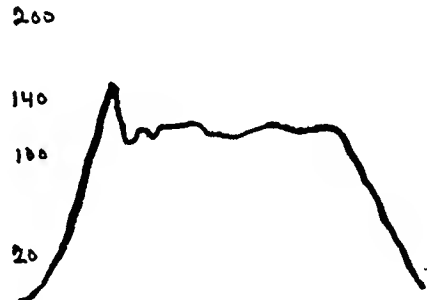


Fig. 9.

Fig. 8.—Case 2. Third Rubin Test: After twenty-one diathermy treatments, the pressure rose to 160 mm. of mercury and then dropped to 120 mm. and then rose again to 140 mm. and fluctuated around 140 mm. The patient complained of pain in the left lower quadrant during the test and of severe right shoulder pain when sitting up.

Fig. 9.—Case 2. Fourth Rubin Test: After twenty-four diathermy treatments, the pressure rose to above 170 mm. of mercury and gradually dropped to 140 mm. with very weak tubal contractions. The patient complained of pain in both lower quadrants during the test but no shoulder pains when sitting up.

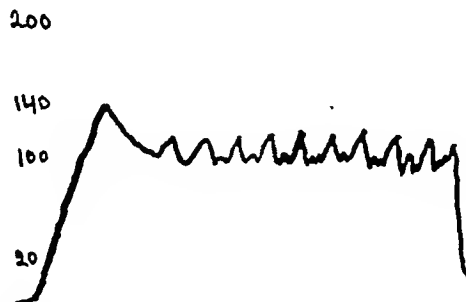


Fig. 10.—Case 2. Fifth Rubin Test: After thirty diathermy treatments, the pressure rose to 140 mm. of mercury, gradually dropped to 120 mm. and then fluctuated around 100 mm. with fairly normal tubal contractions. The patient complained of pain in the left lower quadrant during the test and severe right shoulder pain upon sitting up.

CASE 5.—S. D., aged thirty-six, married eight years, had an abortion five years ago at two months, followed by dilatation and curettage. This patient had been

which occur in individuals over forty years of age is not very satisfactory, even from a theoretical point of view.

As will be shown later in the irradiated ovary of the mouse, although the changes that occur are not entirely comparable to what takes place in the human ovary and are therefore only suggestive, the granulosa tumors are derived from surviving granulosa cells of the fully differ-

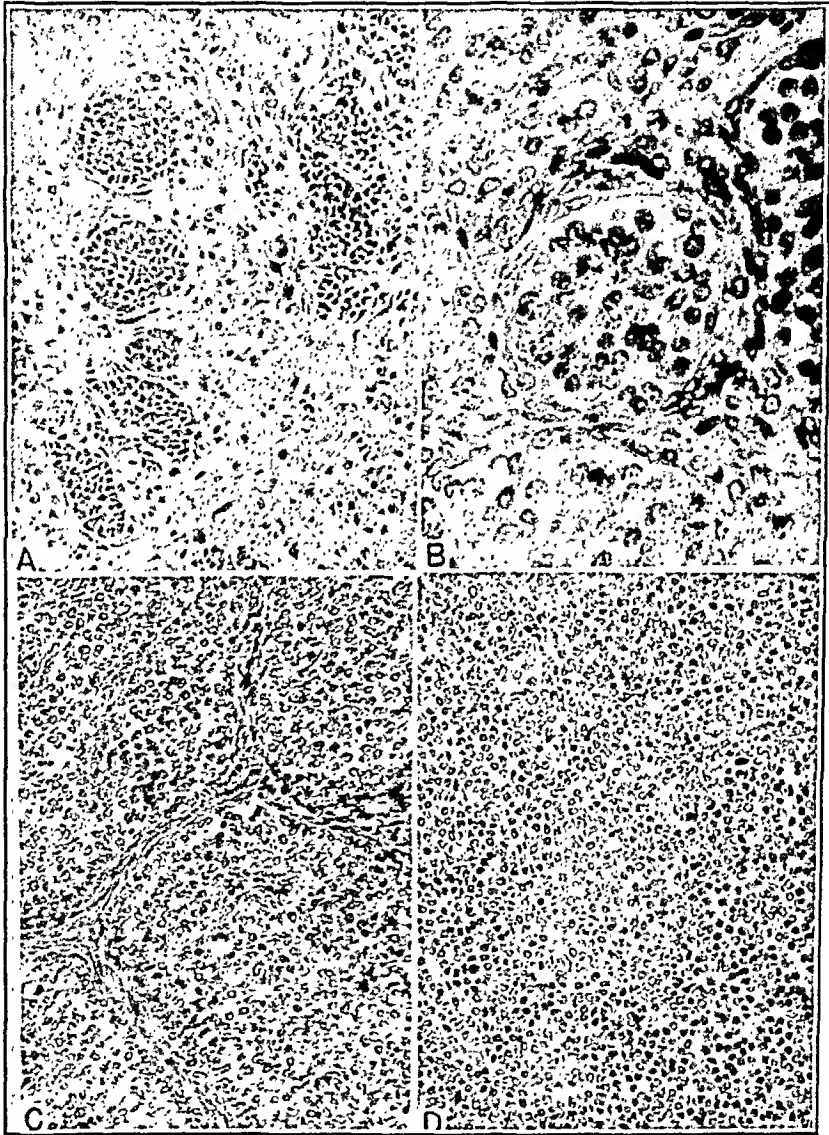


Fig. 5.—Granulosa tumors of the mouse ovary. A, Very early granulosa growth after irradiation with x-ray, showing growth among degenerated granulosa, theca and lutein cells. B, Later stage of growth showing proliferation of granulosa cells in cylindromatous pattern. C, Much later, large cylinders of solid cells. D, Solid pattern, no differentiation.

entiated adult ovary. Furthermore, the luteomas are formed by luteinization of the granulosa tumors thus produced. The possibility, therefore, suggests itself that even in the human being, some granulosa cells of the follicular system may survive the menopause and under some unknown stimulus develop into tumors. Or it may be that the

It has also been generally accepted that the tumors we are considering did not arise in the human ovary from normally differentiated theca, granulosa, or lutein cells. Instead, it has been thought, following the teachings of Robert Meyer and Walthard, that they were formed from unused nests of partially differentiated cells called "Granulosaballen" surviving the period of embryonic development.

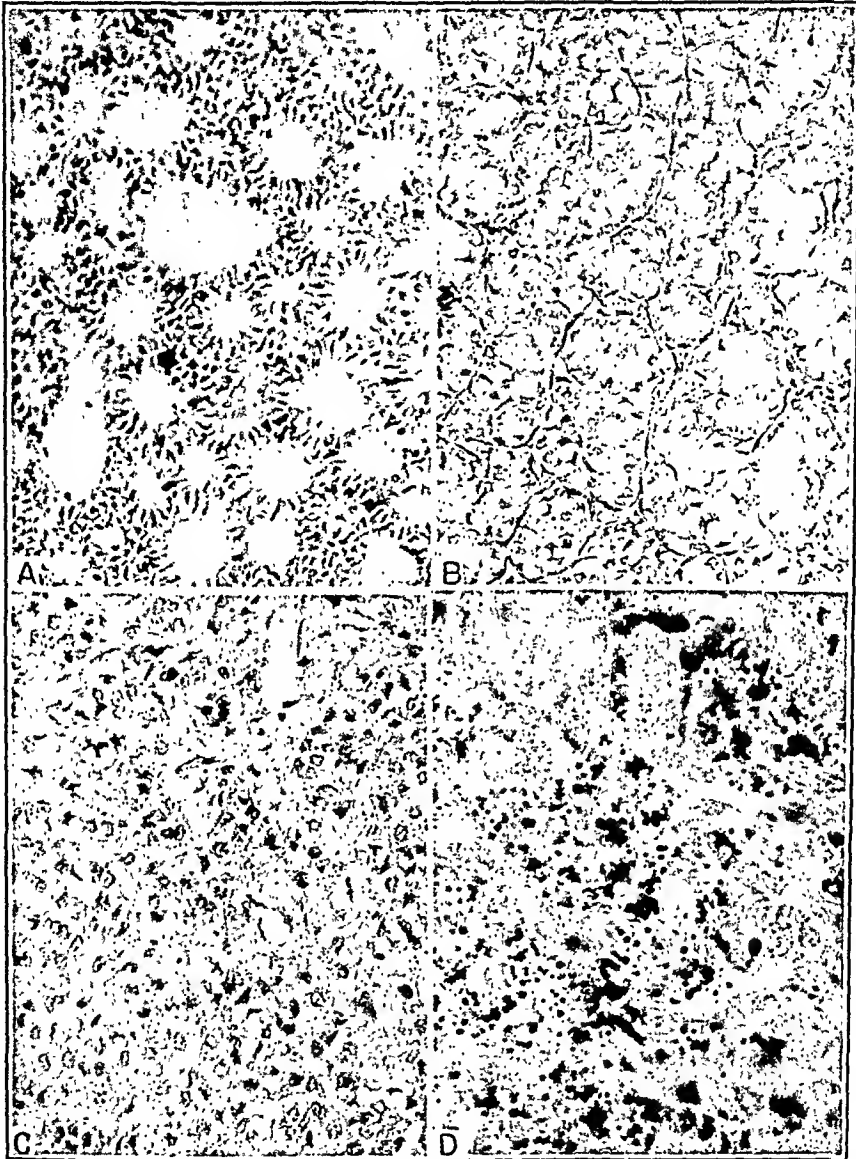


Fig. 4.—Lutein tumors of the human ovary. A, Partially luteinized granulosa tumor (diffuse type of Lecène). B, Completely luteinized portion of a granulosa tumor (general type of Lecène—folliculome lipidique). C, So-called "luteoma." Certainly an ovarian tumor of lutein cells, but in all probability a luteinized granulosa tumor. Occasional granulosa cells are still seen. D, Luteinized tumor stained with Sudan III to demonstrate intra- and extracellular fat droplets.

These "Granulosaballen" or "Granulosaschläuche" are frequently seen at the hilus of the fetal ovary and occasionally in the ovaries of children. Only a few instances have been reported in which they have been observed in the adult ovary, and none in that of the postmenopausal woman. This explanation of the etiology of tumors most of

Furth and Butterworth have recently reported a series of 57 ovarian tumors which they induced by exposing sexually mature female mice to 190 kilo., 30 ma. of x-ray radiation at 50 cm. distance through 0.5 mm. of copper plus 1 mm. of aluminum filtration. These animals were allowed to live to senescence and died of relatively natural causes. Thus the period of growth of the tumor following radiation was of various durations. Another series of 65 mature animals has been studied by sacrificing them at progressively increasing periods of time following radiation. The postradiational time varied in this group from 3 to 787 days. Both series of tumors will be described in greater detail in other papers. Dr. Furth has very kindly allowed us to study and make photographs of this large material, a privilege which is very gratefully acknowledged.

A study of the first group of ovarian tumors at once revealed a striking resemblance not only morphologically but from an endocrinologic point of view as well, to the various forms of tumors seen in the granulosa series in the human being, with the exception of the theca cell tumor. The mode of development of these new growths and an interpretation of their origin and relationship is possible only in the second series in which the ovarian changes were graduated as to time interval after irradiation.

CHANGES IN THE MOUSE'S OVARY FOLLOWING X-RAY RADIATION

In general it may be said that the reaction of the cells of the ovary to radiation depends upon their degree of maturity, on the one hand, and their degree of differentiation, on the other. A few of the animals were not quite mature sexually at the time of radiation. In these animals the effect of the rays was more depressing to all cells than in the older animals. In the sexually immature mice, the ovary was reduced to a fibromatous atrophic organ with no surviving epithelium or differentiated stroma excepting the peripheral ovarian epithelium. In the mature animals the ova were the first cells to degenerate and were followed more or less completely by the granulosa, while the theca cells, germinal epithelium, and lutein cells withstood radiation to the extent of survival. The lutein cells degenerate very slowly and show only slight signs of proliferation, whereas, in the granulosa and germinal epithelium, subsequent proliferation is tremendous.

It may be said, therefore, that the radiation effect produces (1) degeneration of all ova; (2) partial degeneration of the granulosa; (3) only slight effect on the theca and lutein cells; and (4) stimulates proliferation of the germinal epithelium and the granulosa cells. The degenerative phase lasts about 150 days after which the proliferative phenomena occur on the part of the granulosa and germinal epithelium.

The proliferation of the germinal epithelium takes place at first on the periphery of the ovary and subsequently produces invaginations

granulosa tumors in the postmenopausal woman have a prolonged growth period and that they commence to grow at or about the climacterium, finally developing to considerable size only at a very much later period.

GRANULOSA CELL AND LUTEIN CELL TUMORS IN MICE

Much is to be learned of the interrelationship of these tumors by a study of experimentally produced ovarian tumors in mice. Several

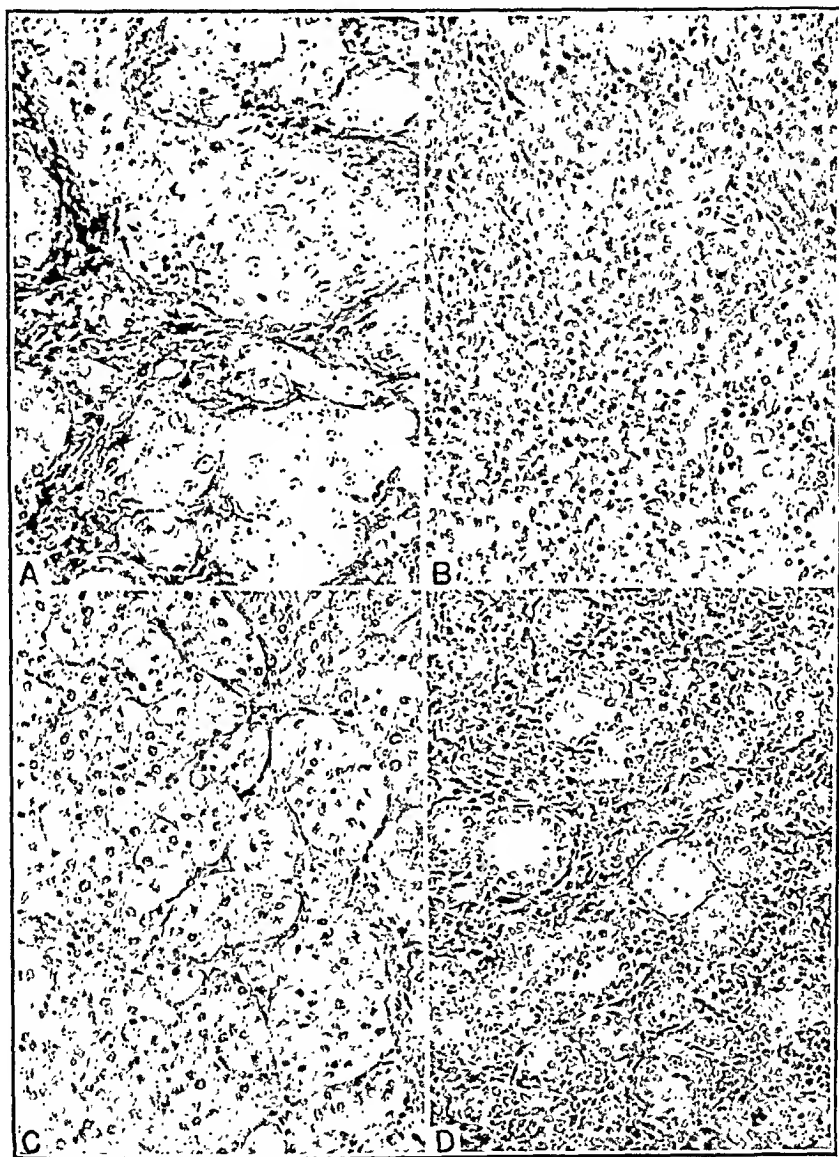


Fig. 6.—*Lutein tumors of the mouse ovary.* A, Localized luteinization with some degeneration in a cylindromatous granulosa tumor. B, Diffuse luteinization in a solid type of granulosa tumor. C, Compare with Fig. 4, B. This is a luteinized granulosa tumor in the mouse. D, Granulosa tumor showing tubular arrangement with very early luteinization.

allusions to our findings in these growths have already been made in various connections. However, it seems necessary to give these in a more complete and logical manner, as an understanding of the human tumors is immeasurably helped thereby.

tion of these growths in the mouse to that probably obtaining in the woman, it may be supposed that the hyperplasia was the result of the fully mature granulosa cell bodies which then further differentiated to form lutein cells with continued estrin secretion. No unquestionable secretory phase was seen with any granulosa tumor in mice, and only a few luteomas produced this progestin effect in the endometrium.

SUMMARY

Theca cell, granulosa cell, and lutein cell tumors are closely related etiologically and physiologically.

Each of these types of tumors possesses the capability of assuming a variety of growth forms and degrees of cellular differentiation. The theca cell tumor exists in two forms: unluteinized and luteinized, the latter being the one commonly described. In its luteinized form it resembles the diffuse type of luteinized granulosa cell tumor in which there is much fibrous connective tissue. The luteinized granulosa cell tumor in which the cells are closely packed with little intervening fibrous connective tissue has close morphologic resemblance to the luteoma and is probably the only way in which true luteoma can arise, as we have seen only slight evidence of growth in lutein cells. They all secrete estrin and have a similar physiologic effect on the uterus. Whether in addition, the luteinized forms secrete progestin has not been proved. The secretory endometrium reported to have accompanied some granulosa cell tumors as well as the prolonged amenorrhea associated with most of the luteomata strongly suggests that progestin is secreted by these tumors under certain conditions.

The ultimate etiology of these tumors is still in doubt. Whether they are derivatives of coelomic epithelium or whether they come from ovarian mesenchyme remains to be proved. However, the evidence for a coelomic epithelial origin becomes progressively weaker as new information is brought to bear upon the subject.

The belief that the tumors cannot arise from surviving adult granulosa cells is also in doubt. The evidence from our mouse tumors, though not conclusive, points definitely to the possibility that they may arise in this way. Thus the "Granulosaballen" theory of Robert Meyer is placed in greater doubt than has formerly been the case.

That the granulosa cell tumor can become luteinized either diffusely or locally has been demonstrated. This process occurs and explains satisfactorily the occurrence of the Lecène type of tumor and probably the luteoma as well.

With more careful hormonal studies and examinations of the endometrium in patients carrying luteomas and partially luteinized granulosa tumors, we should expect to find more frequent evidence of progestin activity.

into the substance of the ovary toward the hilum which, if the animal lives 300 to 400 postradiational days, develop into a form of germinal epithelial adenoma which has no hormonal significance and no relation to the granulosa series of tumors. That there is no connection between the proliferation of the surface epithelium and the subsequent development of the granulosa or lutein type of tumor is a conclusion that is reached after careful study of many sections of these tumors. Special thought was given this point because of the Pflüger-Waldeyer theory of the origin of granulosa cells and because of the conclusions of Bramwell, Parkes and Fielding who, in studying infantile animals after radiation, thought that there was such a relationship. In these series of sexually mature animals no definite relationship was found to exist.

The development of the granulosa and lutein tumors took place from surviving granulosa cells and perhaps from theca cells.

The nests of growing granulosa cells can be seen proliferating in the acinus of the partially degenerated follicle. In some the growth is rapid, forming a solid mass of cells similar in every way to the cylindromatous type in the human tumor. In others a small rosette arrangement with a small central area of degeneration simulates the Call and Exner bodies. Occasionally the degeneration of the central area is more complete, the cells being replaced by fluid corresponding to the *folliculoma* type of growth seen in the human tumors. In other areas the proliferation of cells extends in the connective tissue planes and results in a trabecular disposition of the tumor.

Luteinization occurs diffusely as in the Leeéne type of tumor and also in massive foci forming true luteomas. Finally, even the rare tubular arrangement of the granulosa cells was seen in these mouse tumors.

EVIDENCE OF ENDOCRINE ACTIVITY IN MOUSE GRANULOSA TUMORS

It is a well-recognized principle among pathologists that morphologic analogy is not sufficient evidence to establish identity. Therefore, physiologic activity may give important additional evidence to establish the similarity of the mouse to the human tumor. There is every reason to believe that the granulosa cell tumors which develop after radiation in the mouse's ovaries are, if not identical, at least very similar to the human tumors. This conclusion is based upon morphologic similarities and the fact that the uterus, especially the endometrium, reacts to their presence by developing a hyperplastic endometrium. In one animal the uterine wall was penetrated by the endometrium and true adenomyosis was observed.

The luteomas were possibly somewhat more usually associated with the hyperplastic phenomenon in the uterus than the granulosa cell tumors. At first this may seem contrary to what is usually seen in human tumors. However, if one compares the relatively short dura-

the original circle of cells. The vast mass of the ovary which is so frequently called stroma, but which I prefer to call parenchyma, contains not only connective tissue elements but a vast number of differentiated mesenchymal cells which have the potentiality to become either granulosa or theca or possibly other cell types, and I believe that it is from these parenchymal cells that the granulosa and theca cell neoplasms arise. This concept would more readily explain why such tumors develop after the menopause, when the follicles have degenerated and the follicular epithelial growth no longer exists. The parenchyma undoubtedly contains structures capable of further development when properly stimulated. What the stimulus is at the present time is unknown. The slides that Dr. Traut demonstrated of the mouse tumors seem to me to add weight to the concept of the histogenesis of the granulosa and theca cell type of tumors.

It is possible that one may get combination tumors such as the following: The patient was past the menopause and complained of bleeding. Robert Meyer, who saw sections of the growth, thought that the tumor might be an arrhenoblastoma but hormonal study of the tumor tissue showed that it contained a considerable amount of estrin. It is perfectly reasonable to suppose that a tumor can be composed of two components responding to a common stimulus and the result of such a growth might be a tumor presenting characteristics of each type. In the instance above quoted the possibility of an arrhenoblastoma in association with a granulosa cell tumor can be entertained. The symptomatology may at times be confusing. We may have a clinical picture which does not conform to the type we anticipate, such as the masculinization associated with the tumor of the granulosa cell type, but it is only a question of time when the clinician and laboratory worker will have sufficient material to enable him to classify these growths.

Dr. Traut suggests that luteoma represents the luteinization of either a granulosa cell tumor or a theca cell tumor, and with that concept I am entirely in accord. I do not believe that the tumor can arise from a completed granulosa lutein cell. The term granulosa lutein cell is applied to a granulosa cell that has undergone a definite lipid change, and such cells if they were capable of reproduction would reproduce as normal granulosa cells and not as luteinized cells. Yet, I believe that in many instances the tumors that have been reported as luteomas were either metastatic hypernephroma or tumors arising from aberrant adrenal cortical tissue. Furthermore in many instances the symptom associated with luteoma strikingly resembles the symptom complex associated with adrenal cortical neoplasm. One so-called luteoma that I had an occasion to examine and which had been reported in the literature turned out to be a Krukenberg tumor.

DR. HOWARD C. TAYLOR.—Dr. Traut and Dr. Geist have covered the embryologic aspects of this subject exhaustively. I wish, therefore, to make a few clinical points in regard to the frequency of these tumors, and to the symptoms they give rise to.

On the gynecologic service of the Roosevelt Hospital, there were treated 405 cases of bleeding after the menopause during a fifteen-year period. Of those cases, there were only four that belonged to the group under discussion. Hence if you have a case of postmenopausal bleeding, the chances are, roughly, one hundred to one that a granulosa cell tumor is not present. In the 405 cases, there were in all 23 cases of ovarian tumor. Besides the 4 granulosa cell tumors, there were 8 typical adenocarcinomas of the ovary, and 11 miscellaneous benign tumors, most of them pseudomucinous cystadenoma. Hence if you have a case of bleeding after the menopause even when associated with an ovarian mass, the chances are still five to one that you are not dealing with a granulosa cell tumor.

In view of this work which definitely demonstrates that the x-ray ultimately has a stimulating effect upon the granulosa cells, it may be wise to limit the use of x-ray in the woman to those conditions of such urgency as would justify its use despite this effect. It would seem that x-ray abortion and sterilization were examples of procedures which usually would not have this justification.

The studies of the ovarian tumors of mice have been supported by a grant from the International Cancer Research Foundation.

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DISCUSSION

DR. SAMUEL H. GEIST.—The histogenesis of granulosa cell tumors of the ovary is still a subject of considerable discussion. Fischel's theory that the ovarian parenchyma is the result of the differentiation of the mesenchymal cell mass is being accepted by a large number of embryologists. Fischel's theory is more logical in that it conforms to the accepted belief of the development of other organs.

The ovum is surrounded by a single row of parenchymal cells, i.e. follicular cells and the further development of the follicle cells is the result of the proliferation of

Though it is a little early to formulate a final rule of therapy, the following plan is presented. A well-encapsulated, unilateral, granulosa cell tumor in a woman in the childbearing age, requires only simple salpingo-oophorectomy. If the tumor is bilateral, it has clinically, at least, malignant potentialities. Complete hysterectomy and bilateral salpingo-oophorectomy are indicated. In frankly malignant cases, the treatment should be that of any other ovarian malignancy, surgical removal of as much of the tumor and contiguous tissue as possible, followed by deep x-ray therapy. The reports on the efficacy of the latter agent are contradictory in the literature. The records of dosage are so unsatisfactory that no conclusions appear warranted.

DR. SANFORD KAMINESTER.—The possible effects of irradiation on this tumor in human beings has been brought out. The first tumor Dr. Gordon referred to was some 6 cm. in diameter. Although the uterus showed extensive change as a result of the radium treatment, the ovarian growth had not been affected. We were unable to say whether or not the tumor was present at the time radium was first employed.

In another case at the Long Island College Hospital, the patient had postmenopausal bleeding for which she was treated with radium. At the time, she presented no evidence of any tumor. Six months later, however, there was a large mass in the pelvis. When it was removed, the mass was found to be a granulosa cell carcinoma. This patient died within eight weeks of operation.

EXPERIENCE IN THE TREATMENT OF CARCINOMA OF THE FUNDUS OF THE UTERUS, WITH FIVE-YEAR END-RESULTS IN FORTY-SEVEN PATIENTS*

LEWIS C. SCHEFFEY, M.D., AND WILLIAM J. THUDIUM, M.D.,
PHILADELPHIA, PA.

*(From the Department of Gynecology and the Tumor Clinic, Jefferson
Medical College Hospital)*

THE experiences here related concern 68 consecutive patients admitted to the ward and private services of Dr. Brooke M. Anspach and associates, Department of Gynecology, Jefferson Medical College Hospital, from Sept. 1, 1921, to Sept. 1, 1936, in each of whom a diagnosis of carcinoma of the uterine fundus was substantiated histologically. The study provides a basis: first, for a review of certain points of general interest relative to the entire group; second, for a discussion of the treatment and end-results observed in a five-year series totaling 47 patients. There are no untraced patients.

AGE INCIDENCE, PARITY, AND RACE

On admission, 55 patients were between the ages of fifty and seventy (80.9 per cent). Thirteen were under the age of fifty (19.1 per cent). The youngest patient in the series was thirty-seven, the only one in the group under forty years of age; the oldest was sixty-nine. Two patients were Jewish; only one was a negro. Twenty-five were nulliparous (36.7 per cent), of whom 13 were unmarried.

*Read at a meeting of the Obstetrical Society of Philadelphia, March 4, 1937.

When you have this combination of a palpable ovarian tumor with bleeding in the postmenopausal period, the bleeding may be due to several causes. In the first place, if you have a carcinoma of the ovary, you are liable to have an associated carcinoma of the endometrium. The bleeding is then due to the endometrial and not to the ovarian lesion. In the second place, a certain number of uteri with ovarian tumors bleed, in spite of the fact that the endometrium is atrophic. Various explanations have been given for this. Possibly the presence of a large tumor in the pelvis produces congestion of the blood vessels of the endometrium. There is a suggestion in the literature that some of the nonspecific tumors have some effect finally on the endometrium, such as one or two reports of hyperplastic changes in the endometrium associated with pseudomucinous cystadenoma. (Lantern slide demonstration of 4 tumors of granulosa cell group.)

DR. ONSLOW A. GORDON, JR.—The clinical diagnosis of these tumors is not as a rule difficult when they occur before puberty or after the menopause. When they originate during active sexual life the diagnosis is much more difficult. After the menopause, the first procedure is curettage, and in most of these cases this will reveal a definitely hyperplastic endometrium without evidence of malignancy. With postmenopausal bleeding of a somewhat regular type, not irregular spotting or scant metrorrhagia, associated with a hyperplasia of the endometrium, one is fairly well justified in making a diagnosis of granulosa cell tumor.

In each of two cases of granulosa cell tumor I have recently seen there had been a provisional diagnosis of carcinoma of the corpus, but curettage of each yielded a definite hyperplastic endometrium. One of these patients subsequently came into the Gynecological Service at Long Island College Hospital and has been reported by Drs. Kaminester and Wolfe. That patient had a curettage followed by intrauterine radiation and x-ray, but the bleeding recurred and a granulosa cell tumor was later removed.

The second patient was first seen in 1926 when fifty years of age, suffering from menorrhagia of a regular type. She had not passed through the menopause. The uterus was definitely myomatous, about the size of a three months' gestation. Because of a recent operation for cholecystitis, it was thought unwise to treat her menorrhagia by laparotomy, and so she received x-ray radiation. This controlled her bleeding and produced an absolute amenorrhea of eight years' duration. In 1934, when fifty-nine years of age, she began to have metrorrhagia resembling somewhat menstruation in type and a diagnostic curettage was done. The histologic findings showed simply hyperplasia of the endometrium with no evidence of malignancy. At the time of curettage radium was introduced into the body of the uterus, and she was given 2,400 mg. hr. intrauterine radiation. Bleeding, however, did not cease entirely. A diagnosis of granulosa cell tumor of the ovary was then made, and in 1935 she had a complete hysterectomy with a bilateral salpingo-oophorectomy. The unilateral ovarian tumor measured 6 cm. in diameter and was classified as a granulosa cell tumor growth. This case is very interesting and emphasizes the point made recently by Studdiford that many of these tumors are exceedingly radio-resistant.

DR. SAMUEL A. WOLFE.—The need for the study of the criteria of malignancy in this group is shown by the varying reports on the frequency of malignant examples. In Schiller's series of 24 cases, 8, or 33 per cent, were malignant. In Habbe's series of 70 cases, 14 per cent were clinically malignant. In the largest series in this country (Novak and Brauner), there was an incidence of malignancy in 28.1 per cent of the cases. Large numbers of mitotic figures are suggestive. Variation in the size and shape of the nuclei is of special significance only if cells of similar pattern are studied.

sterile ever since. The menses began at the age of fifteen, every three weeks, lasting two days with a moderate amount of flow. Slight backache the first day of each period.

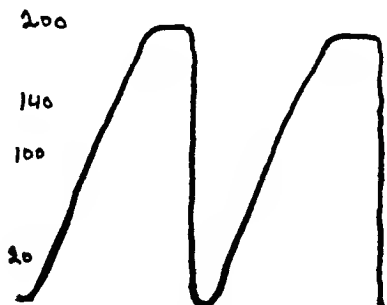


Fig. 11.

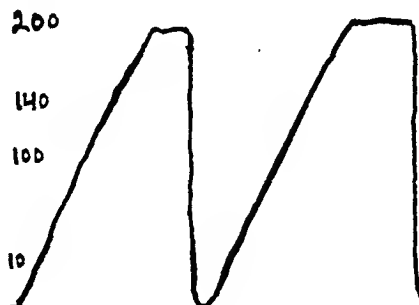


Fig. 12.

Fig. 11.—Case 3. First Rubin Test: The pressure rose twice to 200 mm. of mercury and each time was maintained for half a minute. The patient had pain in both lower quadrants during the test; but no shoulder pains when sitting up.

Fig. 12.—Case 3. Second Rubin Test: After eight diathermy treatments the pressure rose twice to 200 mm. of mercury; the first time the pressure was kept at 200 mm. for half a minute; the second time for a full minute. The patient had pain in both lower quadrants during the test; but no shoulder pains when sitting up.

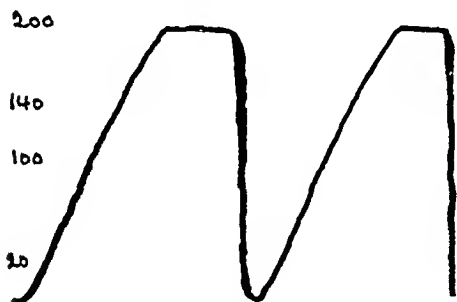


Fig. 13.



Fig. 14.

Fig. 13.—Case 3. Third Rubin Test: After twenty-four diathermy treatments the pressure rose to 200 mm. of mercury and was maintained the first time for one minute and the second time for three-quarters of a minute. The patient had pain in the right lower quadrant during the test; but no shoulder pain when sitting up.

Fig. 14.—Case 3. Fourth Rubin Test: After thirty-six diathermy treatments the pressure rose to 180 mm. of mercury and gradually dropped to 160 mm. and then to 140 mm. with very slight tubal contractions. The patient had pain in the right lower quadrant during the test and pain in the right shoulder one hour after the test.



Fig. 15.—Case 3. Fifth Rubin Test: After forty-three diathermy treatments the pressure rose to 170 mm. of mercury and gradually dropped to 140 mm.; with very faint tubal contractions. The patient had slight pain in the right lower quadrant during the test; and pain in the right shoulder two hours after the test.

Vaginal examination showed a slightly enlarged uterus in anterior position, freely movable. Both adnexa were thickened but not tender. Smears for gonococci were negative.

The proportion of patients with fundal carcinoma admitted to the ward service, when compared with those admitted with cervical carcinoma during the same period, was 1:9.58 (Table I).

TABLE I. AGE INCIDENCE, PARITY, RACE

DECADE	PATIENTS	PER CENT
30-39	1	1.5
40-49	12	17.6
50-59	32	47.1
60-69	23	33.8
Total	68	100.0
Youngest, 37; oldest, 69		
Nulliparas, 25; 36.7 per cent (13 unmarried)		
Negro, 1; 1.5 per cent		
Ratio of carcinoma of cervix (ward service) 1:9.58		

MENOPAUSAL RELATIONSHIP

Sixteen patients (23.5 per cent), whose average age was 47.1 years, had experienced no cessation of periodic bleeding prior to the onset of symptoms, and for practical purposes are regarded as a premenopausal group. However, 6 of these patients were over fifty years of age, and it is quite possible that what they regarded as regular menstrual periods were in fact intermittent periods of bleeding associated with their malignant disease.

Fifty-two patients (76.5 per cent), whose average age was 58.8 years, had definitely passed the menopause when symptoms began, within one to fifteen years thereafter in 80 per cent of cases. In 3 instances symptoms did not make their appearance until twenty to thirty years after the established menopause (Table II).

TABLE II. MENOPAUSAL RELATIONSHIP

GROUP	PATIENTS	PER CENT	AVERAGE AGE
Premenopausal	16	23.5	47.1 yr.
Postmenopausal	52	76.5	58.8 yr.

SIGNIFICANCE AND DURATION OF SYMPTOMS

Irregular uterine bleeding of some variety was the principal symptom exhibited by 95.6 per cent of all the patients. It varied from slight bleeding or bloody discharge ("spotting") to frank hemorrhage. In the premenopausal group, metrorrhagia and menorrhagia were equally divided in frequency; among the postmenopausal patients, "spotting," gradually increasing in amount and frequency, was of most significance. In only 3 patients (4.4 per cent) was there no irregular bleeding of any sort, the initial symptom in one patient being a metastatic nodule in the anterior vaginal wall, appearing ten years after the menopause. Among those patients in whom menstruation had not yet ceased, the duration of symptoms prior to treatment averaged 9.5 months; in the postmenopausal group it was 15.2 months. Approximately one-third of the patients (33.8 per cent) sought advice from one to six months after the irregularity began.

The significance of vaginal discharge and its diagnostic importance is difficult to evaluate.

Nearly half of the patients (47 per cent) emphasized the occurrence of discharge, over periods of months or years, but its diagnostic import was of minor character when compared with the predominant symptom of unusual bleeding.

Pain was likewise complained of by about half of the patients (47 per cent); it was not identical with the group complaining of discharge. With the exception of those patients presenting advanced lesions, responsibility might well be assigned to other causes: associated pelvic lesions, intestinal disturbances, extrinsic factors (i.e. bladder irritability, osteoarthritic manifestations) or to the infirmities of advancing years: diverse annoyances, simply interpreted by the patient as "pain." It is not rational to believe that localized malignancy of the fundus, per se, even though progressive, can initiate pain of diagnostic significance (Table III).

TABLE III. SIGNIFICANCE AND DURATION OF SYMPTOMS

GROUP	PATIENTS	IRREGULAR BLEEDING	AVERAGE DURATION	DISCHARGE	PAIN
Premenstrual	16	14	9.5 mo.	8	6
Postmenopausal	52	51	15.2 mo.	24	26
Total	68	65		32	32
Per cent	100	95.6		47	47

Metrorrhagia and menorrhagia occurring in the premenopausal epoch, and postmenopausal "spotting" or frank bleeding are of primary importance in directing attention to the necessity of excluding carcinoma; leucorrheal discharge and pain are of lesser importance except so far as their presence may influence the patient to seek medical advice.

DIAGNOSIS

The diagnosis was correctly suspected from the symptomatology in 60 patients (88.2 per cent), being confirmed in 54 by diagnostic curettage; in the remaining 6 patients operative treatment was immediately resorted to without curettage, on the basis of the clinical diagnosis and correctly so, as proved by pathologic examination of the removed uteri.

In 19 patients suspected of having carcinoma diagnostic curettage was a preliminary step prior to instituting treatment; in 35 patients, it was carried out at the time of treatment, confirming the strong suspicion of cancer. (In 4 patients, preliminary curettage had been done elsewhere, the procedure being rechecked in three instances when initial radiation treatment was given, while in one, immediate surgical treatment was favored on the basis of the pathologic slide submitted.)

In 8 patients (11.8 per cent) not suspected of having carcinoma, the value of diagnostic curettage is well illustrated, for in 3 of them the procedure revealed the lesion, and proper treatment was planned accordingly. In 4 patients in whom carcinoma was not suspected, the omission of diagnostic curettage was costly, resulting primarily in incomplete plans of treatment which might otherwise have been avoided. Finally, in one patient, although preliminary curettage was performed routinely, the curettings did not excite suspicion, and it was only when an incision was made that the presence of bilateral ovarian carcinoma, secondary to a fundal lesion, revealed the true state of affairs (Table IV).

TABLE IV. DIAGNOSIS

DIAGNOSIS	PATIENTS	PER CENT	PRELIMINARY DILATATION AND CURETTAGE	NO DILATATION AND CURETTAGE
Suspected	60	88.2	54	6
Unsuspected	8	11.8	4	4

These observations confirm and emphasize the well-recognized value of diagnostic curettage, performed circumspectly, and with due regard for the potential dangers accompanying its use, to which Sampson¹ has so forcefully called our attention.

ASSOCIATED PATHOLOGY

The well-recognized association between uterine fibroids and carcinoma of the endometrium was borne out in this series, being noted in 16 patients (23.5 per cent). On two occasions, in patients in the premenopausal group, fibromyoma was the dominant lesion and treatment was based on this assumption; accompanying carcinoma was not suspected and not recognized until the abdominal cavity was exposed. As noted previously, these were two of the four instances in which preliminary curettage would have avoided an incorrect diagnosis.

Extension of carcinoma to the ovaries, tubes, peritoneum, omentum, or intestine was noted in 9 patients (13.2 per cent). Enlarged pelvic glands, induration of the broad ligaments, adnexal and sigmoidal adhesions were likewise noted one or more times among 9 patients (13.2 per cent). Carcinoma elsewhere, independent of the fundal malignancy, was present in five patients: breast, 3; stomach, 1; sigmoid, 1. Benign ovarian tumors were found three times, benign cervical polyps twice.

Three patients had prolapse of the uterus of varying degree; 2 amounted to complete procidentia, and this association with carcinoma has been reported in a previous communication.²

The association with diabetes is rather surprising. It was an accompanying condition in 7 patients (10.2 per cent). Varying degrees of obesity, cardiorenal and cardiovascular disease were encountered. Three suffered from gallbladder disease; one patient each had chronic pulmonary tuberculosis, chronic phlebitis and hemiplegia, respectively.

It is interesting to note that in 52 patients (77.6 per cent) the hemoglobin estimation on admission was 70 per cent or higher, while 54 patients (81.8 per cent) had red blood cell counts of 3,500,000 or higher. The leucocyte count was under 9,000 in 37 patients (56 per cent); above 9,000 in 29 patients (44 per cent). The lowest count noted was 4,100; the highest 21,300. In view of the comparatively long duration of symptoms presented by most patients prior to treatment, these readings seem peculiarly high in the case of the hemoglobin and red blood cell estimations; the leucocyte counts seem more in keeping with the pathology encountered (Table V).

TABLE V. ASSOCIATED PATHOLOGY

LESION	PATIENTS	PER CENT
Fibromyoma uteri	16	23.5
Carcinomatous extension	9	13.2
Induration and adhesions	9	13.2
Diabetes	7	10.2
Concomitant carcinoma	5	7.3
Benign ovarian cyst	3	4.4
Procidentia	2	2.9
<i>Blood Counts:</i>		
Hemoglobin above 70 per cent	52	77.6
R. B. C. above 3½ million	54	81.8
W. B. C. under 9,000	37	56.0
W. B. C. above 9,000	29	44.0

CLINICAL CLASSIFICATION AND HISTOLOGIC GRADING

We have attempted to classify the degree of involvement according to the grouping suggested by the American College of Surgeons. Upon this basis, 50

patients (73.5 per cent) were in Class 1 A (primary case, disease limited to uterine cavity). Sixteen patients (23.5 per cent) were in Class 1 B (primary case, disease involving broad ligaments [ovary]). The remaining 2 were, respectively, in Class 1 C (primary case, vaginal metastasis) and Class 6 A (recurrence after radiation therapy). This patient was treated elsewhere primarily.

Furthermore, in conjunction with and under the direction of Dr. Baxter L. Crawford, Pathologist and Director of Clinical Laboratories at the Jefferson Hospital, all pathologic material was reviewed in order to estimate the degree of malignancy exhibited in each case. With one exception, in which instance the histologic slide and paraffin block could not be found, every specimen was available for review and study.

In the study of our fundal carcinomas we have divided them into three groups as recommended by various authors: Ewing, Mahle, Healy and Cutler. The low grade (corresponding to papillary adenoma malignum and adenoma malignum, Grades I and II); the intermediate group (corresponding to adenocarcinoma, Grade III); the high grade or extremely anaplastic variety (cellular-anaplastic-adenocarcinoma, Grade IV).

This plan of differentiation placed 22 of the carcinomas in the low grade, 27 in the intermediate, and 18 in the high grade histologic grouping, with one unclassified, for the reason previously stated (Table VI). The question of the relationship of endometrial hyperplasia to fundal carcinoma, and a discussion of the so-called "carcinoid" type of lesion has not been included in this presentation.

TYPE OF TREATMENT

In all, 67 of the 68 patients seen have had treatment. From 1921 to 1931, 46 of 47 patients seen were treated and form the basis for an analysis of five-year end-results. Of 46 cases, 13 (28.2 per cent) were subjected to surgery alone; 18 (39.1 per cent) by radiation (radium alone, or in conjunction with x-ray); 15 (32.6 per cent) by surgery in combination with radiation (preliminary radium, and/or with x-ray, or postoperative x-ray). It is significant that since 1931 no

TABLE VI. CLINICAL CLASSIFICATION AND HISTOLOGIC GRADING

GROUPING AMERICAN COLLEGE SURGEONS	PATIENTS	PER CENT
Class 1 A	50	73.5
Class 1 B	16	23.5
Class 1 C	1	1.5
Class 6 A	1	1.5
<i>Histologic Grading</i>		
Low	22	32.3
Intermediate	27	39.7
High	18	26.4
Unclassified	1	1.6

TABLE VII. TYPE OF TREATMENT

YEARS	PATIENTS SEEN	PATIENTS TREATED	SURGERY	RADIATION	SURGERY AND RADIATION
1921-31	47	46	13	18	15
Per cent			28.3	39.1	32.6
1931-36	21	21	0	15	6
Per cent			—	71.4	28.5

case has been treated by surgery alone; that in 15 patients (71.4 per cent) radiation has been used exclusively, surgery in combination with radiation being the treatment of choice in 6 patients (28.5 per cent) (Table VII).

ANALYSIS OF FIVE-YEAR END-RESULTS

As stated in a previous contribution,³ we re-emphasize our belief that an eight-year limit of freedom from the signs and symptoms of carcinoma is a more desirable criterion of survival than the generally accepted five-year limit, and again suggest that the latter term be qualified by the expression "five-year salvage." We have chosen to evaluate our five-year end-results from two viewpoints:

1. *The General Five-Year Salvage Observed in 47 Patients Seen From 1921 to 1931, Irrespective of the Type of Treatment and Grade of Malignancy.*—Of 47 patients seen, 46 were treated. Twelve are alive and present no demonstrable evidence of recurrent carcinoma, the salvage periods ranging from five to thirteen years, the present ages of the patients varying from fifty-four to seventy-seven years. The present-day salvage therefore is 25.5 per cent absolute and 26 per cent relative. Three additional patients survived from five to eight years, but clinically did not die of carcinoma, increasing the five-year survival period to 31.9 per cent absolute and 32.6 per cent relative. Three patients, who survived from six to seven years after treatment but died of carcinoma, increase the five-year salvage figure to 38 per cent absolute and 39.1 per cent relative, but this is solely of theoretic interest. Twenty-nine patients died of cancer within five years of treatment, most of them within a year, including the untreated case. There were 2 postoperative deaths, a primary mortality for the entire series of 4.3 per cent, or for the patients subjected to hysterectomy, 8.6 per cent (Table VIII).

TABLE VIII. FIVE-YEAR SALVAGE IRRESPECTIVE OF THE TYPE OF TREATMENT AND GRADE OF MALIGNANCY

YEARS	PATIENTS SEEN	PATIENTS TREATED	PRESENT- DAY SALVAGE	5-YEAR SURVIVAL NONCANCER DEATHS	5-YEAR SURVIVAL CANCER DEATHS	PRIMARY MORTALITY
1921-31	47	46	12	3	3	2
Per Cent (Absolute)			25.5	31.9	38.0	4.3 (All cases)
Per Cent (Relative)			26.0	32.6	39.1	8.6 (Hyster- ectomy)
No untraced patients						

2. *Five-Year Salvage in Relation to the Type of Treatment and Histologic Grouping of the Malignancy.*—A. *Low-Grade Group—15 Patients:* Five patients were treated by surgery alone, of whom two have survived the five-year period (40 per cent). They are living six and nine years, respectively, since operation, which was complete abdominal hysterectomy with bilateral salpingo-oophorectomy.

One patient succumbed of general carcinomatosis two months after the complete operation. In another, supravaginal hysterectomy with bilateral salpingo-oophorectomy was performed because technical difficulties (adherent sigmoid) prevented the performance of the planned complete operation. The amputation seemed to be well below the malignant area, and the cervical stump was cauterized from above. Nevertheless the patient died four and one-half years later of metastatic carcinomatosis. Postoperative radiation might have been desirable.

A death, occurring in a woman sixty years old, followed complete abdominal hysterectomy with bilateral salpingo-oophorectomy. On the twelfth postoperative day coma developed and a blood sugar reading of 506 mg. per c.c. was obtained. Although urinalysis prior to operation had been negative, a review of the records showed one positive postoperative specimen, which would indicate that diabetes had probably been overlooked, although at the time her death was attributed to myocardial failure. This fatality might have been prevented had more significance been attached to the postoperative urinalysis.

Five patients were treated by *radiation alone* of whom 2 have survived the five-year period (40 per cent). They are alive and symptom free from six to seven years. One received a single intrauterine application of 5,400 mg. hr.; the other 2,400 mg. hr. followed by one course of x-ray. Three patients died of carcinomatosis within two years. In one of these patients, carcinoma was subsequent to an interposition operation performed two years before. She received 3 intrauterine applications of radium, 300, 3,600, and 2,400 mg. hr., respectively, the small primary dosage at the time of preliminary curettage. The second patient received 2 applications each of 2,400 mg. hr., the third patient receiving 2,400 mg. hr., followed by two courses of x-ray.

Five patients were treated by *surgery in combination with radiation*, of whom 3 survived the five-year period (60 per cent). Two are living and well, seven and eight years, respectively. One remained well of carcinoma but committed suicide eight years after treatment, having developed manic-depressive insanity. Routine curettage in this patient at the time of a plastic and ventral fixation operation, revealed carcinoma. Three thousand six hundred mg. hr. of radium were applied to the uterine cavity followed in eight weeks by complete abdominal hysterectomy with bilateral salpingo-oophorectomy. Necrosis of the uterine cavity, but no evidence of carcinoma was found in any of the removed organs. In the case of the 2 surviving patients, supravaginal hysterectomy with bilateral salpingo-oophorectomy was employed because of technical difficulties encountered (in one, induration of the broad ligaments; in the other, poor reaction to anesthesia), although the diagnosis had been established by preliminary curettage and complete operation planned. In both instances the supravaginal amputation was well below the carcinomatous area and the cervical stump was cauterized from above prior to peritonization. Postoperative x-ray followed in each instance.

Two patients survived from six to seven years but died of carcinoma. In one, the possibility of carcinoma was not recognized grossly in the preliminary curettage, and abdominal section was immediately proceeded with because of the presence of an abdominal tumor. Bilateral ovarian carcinoma was found and removed, and supravaginal hysterectomy was performed. Routine histologic examination revealed fundal carcinoma as well, and 3,000 mg. hr. of radium were subsequently applied to the cervical stump. This patient was lost sight of, only to return seven years later with uremia and generalized abdominal carcinomatosis, proved at autopsy. Postoperative x-ray therapy might possibly have prevented this outcome. In the second patient, preliminary radium and x-ray was followed by complete abdominal hysterectomy with bilateral salpingo-oophorectomy. There was no evidence of carcinoma in the removed organs, but death was eventually due to carcinomatosis.

B. Intermediate Grade Group—19 Patients: Five patients were treated by *surgery alone*. Only one survived the five-year period (20 per cent); this patient, treated by complete abdominal hysterectomy with bilateral salpingo-oophorectomy, succumbed of intercurrent disease. A vaginal hysterectomy in a patient with moderate descensus uteri, performed without preliminary curettage, resulted in the removal of a carcinomatous uterus, but not of the adnexa, and the patient died within one year of carcinomatosis. The omission of postoperative radiation is re-

grettable, while preliminary curettage might have resulted in complete operation or a different plan of treatment. Two patients having complete abdominal hysterectomy with bilateral salpingo-oophorectomy succumbed within one year from carcinomatosis.

There was one postoperative death in this group. The patient was forty-seven years old, and the preoperative diagnosis was fibromyoma uteri. Without preliminary curettage, supravaginal hysteromyomectomy with bilateral salpingo-oophorectomy was performed. When fundal carcinoma was discovered in the amputated uterus, the cervical stump was immediately cauterized from above and removed, but death from peritonitis occurred on the seventh postoperative day. Preliminary curettage would probably have indicated a different plan of treatment.

Eight patients were treated by *radiation alone*. Three have survived the five-year period, five, eight, and thirteen years, respectively. One received a single radium treatment (3,600 mg. hr.), while one at the time of diagnostic curettage, received 200 mg. hr., pending the report on the curettings, after which a second application (3,600 mg. hr.) was made. The third received 2,400 mg. hr. of radium followed by one course of x-ray. Two patients, each receiving single applications of 2,400 mg. hr., died within three years: 2 patients, one receiving 4,800 mg. hr. and one course of x-ray, and the other 3,000 mg. hr. and two courses of x-ray, followed by more intrauterine radium (900 mg. hr.) and 600 mg. hr. for vaginal metastases, died within one year. One patient, with concomitant carcinoma of the breast, received one course of deep x-ray therapy only, surviving three and one-half years.

Five patients were treated by *surgery combined with radiation*, of whom one has survived eleven years (20 per cent). The procedure was complete abdominal hysterectomy with bilateral salpingo-oophorectomy followed by x-ray. Two patients, having the complete operation followed by x-ray, died of carcinomatosis within one and four years of operation, respectively. A third patient received intrauterine radium and x-ray prior to operation, which revealed abdominal carcinomatosis with extension to the right tube and ovary which latter organs only were removed. Further x-ray was employed postoperatively. Strangely enough, she survived six years, before dying of carcinoma. In the case of one patient, in whom preliminary curettage was omitted, supravaginal operation for fibromyoma revealed not only carcinoma of the endometrium following the uterine amputation and bilateral salpingo-oophorectomy, but an infiltrating growth in the right broad ligament as well. Radium was applied to this area and postoperative x-ray employed. Three months later the patient died of lobar pneumonia and autopsy demonstrated the persistence of carcinoma in the pelvis.

One untreated patient died of carcinomatosis within four months.

C. High Grade Group—12 Patients: Two patients were subjected to *surgery alone* with no survivals. One had received intrauterine radium elsewhere three years before. The reason and dosage could not be ascertained. Complete abdominal hysterectomy with bilateral salpingo-oophorectomy was followed by death from spinal metastasis within a year. The second patient had been subjected elsewhere to 2 intrauterine applications of radium during a period of four years prior to admission, but no histologic study of the curettings had been made and the diagnosis could not be secured. Following a positive curettage, abdominal section revealed carcinomatosis involving the tubes, ovaries, intestines, and omentum. One tube and ovary only could be removed, and the patient died shortly thereafter.

Five patients were treated by *radiation alone*, of whom 2 have survived the five-year period (40 per cent). One is living and well, eight years after treatment (2,400 mg. hr.). The second patient received 3 applications of 2,400, 3,600, and 4,800 mg. hr., respectively, with 2 intervening courses of x-ray. She survived eight years, dying of cardiorenal disease complicating chronic pulmonary tuberculosis from which she suffered when first seen. The remaining 3 patients died within

three and one-half years of treatment. One had received a single treatment (2,200 mg. hr.); a second, two treatments (2,400 and 1,200 mg. hr., respectively); the third a single treatment (7,200 mg. hr.) followed by further radiation elsewhere.

Five patients received *surgical treatment with radiation* in addition. None have survived the five-year period. One patient (aged forty-three) had been treated elsewhere with radium seven years before for functional bleeding. Following complete operation (without curettage), vaginal metastasis and death occurred within a year, with intervening postoperative radiation. A second patient (aged forty-two) had also received radium elsewhere nine years before for functional bleeding. Following preliminary intrauterine radiation (2,400 mg. hr.) complete abdominal hysterectomy, with right salpingo-oophorectomy was performed. The left adnexa, adherent to the sigmoid, was of necessity allowed to remain in situ. The endometrial cavity was necrotic but invasion of the uterine wall was present. Two courses of postoperative x-ray were employed, death from carcinomatosis occurring within three years. A third patient (aged forty-five) received 2,400 mg. hr. of radium preoperatively, followed by complete operation. Although the endometrium was necrotic and there was no evidence of carcinoma in the uterus, metastasis in one ovary was found. Postoperative x-ray was followed by death from metastatic carcinomatosis within a year. Operation was abandoned in 2 patients after the abdomen was opened, radium (3 applications: 5,100 mg. hr., 1,200 mg. hr., 2,400 mg. hr., respectively) and x-ray being employed in one, and x-ray only in the other.

The patient whose histologic slide was not available for classification has survived treatment twelve years and is quite well. It is unfortunate that both the block and slide are missing, for it would be desirable to know the specific characteristics of the adenocarcinoma in this instance. We hope that continued search will be successful for use in subsequent reports (Table IX).

TABLE IX. FIVE-YEAR SALVAGE IN RELATION TO THE TYPE OF TREATMENT AND HISTOLOGIC GROUPING OF MALIGNANCY

GRADE OF MALIGNANCY	SURGERY	RADIATION	SURGERY AND RADIATION	5-YEAR SALVAGE GRADE OF MALIGNANCY
Low	2 of 5 40%	2 of 5 40%	3 of 5 60%	7 of 15 46.6%
Intermediate	1 of 5 20%	3 of 8 37.5%	1 of 5 20%	5 of 18 27.7%
High	0 of 2 —	2 of 5 40%	0 of 5 —	2 of 12 16.6%
Five-year salvage, type of treatment	25%	39%	20.6%	

(One surgical patient surviving twelve years has been unclassified histologically)

DISCUSSION

The radium employed was screened with 0.3 mm. of silver, 1.0 mm. of brass, and protected with 2.0 mm. of black rubber tubing. The x-ray therapy has been and is carried out in the Department of Roentgenology at Jefferson Hospital with the cooperation of and under the direct supervision of the late Dr. Willis F. Manges, and his associates Drs. John T. Farrell, Jr., and Manges Smith. The technic has been described in detail in a recent contribution.³ Since August, 1927, the factors used in the treatment are 200 kilovolts, 50 cm. distance filtered

through 0.5 mm. of copper and 1.0 mm. of aluminum. The output on the machine is 18.5 r. per minute when 8 ma. are used and the erythema dose is estimated at 800 r. The dosage delivered through each port by this method varies from 1400 to 2500 r.

During the earlier years covered by this report, complete operation was thought to be the treatment of choice for carcinoma of the fundus. Patients obviously not suited for surgery were treated with radium and x-ray. In 1926 we began definitely to combine surgical treatment with radiation therapy. Radium was then used as a preliminary procedure, and complete hysterectomy was sometimes followed by x-ray postoperatively. A plan of treatment evolved at that time and continued with some modification is at present as follows: When a patient is seen in whom carcinoma of the fundus is suspected, diagnostic curettage is carried out and 50 or 100 mg. of radium are available for intrauterine application. If a frozen section of the curettings establishes the diagnosis of malignancy beyond question, the radium is allowed to remain in situ for a designated time. Subsequent treatment, whether by further radiation or by combined radiation and surgery, is dependent upon the clinical picture and the grade of malignancy as determined by a thorough study of rapidly prepared (24 hr.) paraffin sections. If an accurate diagnosis cannot be made from the frozen section the radium, usually 50 mg. in this instance, is not removed until the exact diagnosis has been determined from the rapid paraffin section. If carcinoma is not present, the radium therapy that has been employed is usually adequate to control the symptoms.

Furthermore, we have come to the conclusion that if carcinoma has been diagnosed, is clinically limited to the uterus, and the patient is a reasonably good operative risk, that complete abdominal hysterectomy with adnexal extirpation from six to ten weeks after radiation is the preferable procedure, especially if we are dealing with a low grade type of malignancy. Operation by the vaginal route may sometimes be a better plan. The question of giving preliminary x-ray therapy during this time in addition to the radium already applied depends upon the physical characteristics of the patient. It is generally agreed that the obese patient with a thick pendulous abdomen and heavy buttocks, or the extremely thin devitalized individual, is not a good subject for external radiation. It may be wiser in these circumstances to depend upon radium alone for preliminary radiation.

When an intermediate or high grade type of malignancy is present, when the disease has markedly advanced clinically, or when the patient's general condition makes operation definitely hazardous, our experience has shown that radiation may well be regarded as the treatment of choice. It should be stated, however, that individual circumstances may indicate subsequent operation, even though the lesion is of an intermediate or high grade type.

Subsequent test curettage may give a false sense of security, but it is our belief that if after adequate radiation, either with radium alone or combined with x-ray, no bleeding recurs, and none can be provoked by probing the uterine cavity with a sterile sound, the prognosis may be regarded favorably.

From 1931 to 1936 twenty-one additional patients have been seen and treated. Of these 13 are alive for periods varying from one to nearly five years after treatment. Nine are symptom-free, while 4 either show evidence of recurrence or are still under treatment. Eight patients have died within one to three years of treatment. While a detailed analysis of this group would be of interest, time and space do not permit of its inclusion in this presentation.

Observations from this series may be summarized as follows:

1. Four out of 5 women with carcinoma of the fundus developed it after the age of fifty; in 3 out of 4 it was postmenopausal in onset.

2. Irregular uterine bleeding was the predominant symptom. Discharge and pain were of minor diagnostic significance.

3. The advantage of diagnostic curettage outweighs its potentiality for harm. This is especially true of those patients who may develop carcinoma prior to the menopause when more obvious pathology, notably fibromyoma uteri, may appear to be the predominant lesion.

4. Carcinoma of the fundus should be graded as to its degree of malignancy, but as simply as possible. While the folly of attempting to base a prognosis entirely on the gradation of the cell type of growth is obvious, it is plausible to believe that careful consideration of the stage of differentiation of the tumor cells, together with the clinical features of the case, is of distinct value in planning treatment and evaluating the chance of survival.

5. The trend of the results obtained, as presented in this series, is in general accord with the observations of Healy.⁴ The best results, regardless of the type of treatment, were obtained in the low grade malignancy group. Radiation alone gave the best end-results when all groups were considered, and was particularly efficacious in the intermediate and high grade groups. When surgery was employed the results were better when it was combined with radiation. Newell and Crossen,⁵ however, have wisely pointed out the error which may result from the evaluation of results obtained with one form of treatment when compared with that applied to patients exhibiting different clinical stages of the disease.

6. The ultimate prognosis depends upon factors other than the grade of malignancy. Primarily they are clinical and relate to the age and physical condition of the patient, the duration of symptoms, the promptitude of diagnosis, and the extent of the disease. Secondly they relate to treatment. Surgery alone has definite limitations; it should prove more efficacious when combined with radiation.

This patient had four tubal insufflations and 36 diathermy treatments and became pregnant three months after the last tubal insufflation, and gave birth to a normal child (see Figs. 19, 20, 21, and 22).

CASE 6.—L. V., aged twenty-three, married four years, had one abortion six years ago at two months followed by dilatation and curettage. Her menses began at the age of fifteen, every twenty-eight days, of seven days' duration with profuse flow. No pain. Smears for gonococci were negative. Hühner test was positive. Vaginal examination showed a small anteflexed uterus, movable, with thickened adnexa on both sides.

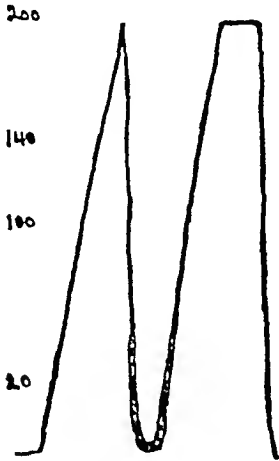


Fig. 16.



Fig. 17.

Fig. 16.—Case 4. First Rubin Test: The pressure rose to 200 mm. of mercury and was allowed to drop. The second time the pressure was kept at 200 mm. of mercury for half a minute. The patient had pain in the center of the abdomen during the test and in the left lower quadrant but no shoulder pains when sitting up.

Fig. 17.—Case 4. Second Rubin Test: After twelve diathermy treatments the pressure rose to 200 mm. of mercury and was maintained for half a minute and then allowed to drop. The second time the pressure rose only to 180 mm. of mercury and gradually dropped to 160 mm., fluctuating weakly around 160 mm. The patient complained of pain in the left lower quadrant during the test and pain in the right shoulder when sitting up.

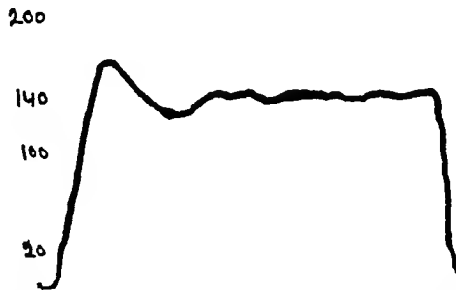


Fig. 18.—Case 4. Third Rubin Test: After twenty-four diathermy treatments the pressure rose to almost 170 mm. of mercury, dropped to 120 mm. and rose again to 140 mm. and fluctuated around 130 mm. with very weak tubal contractions. The patient complained of left lower quadrant pain during the test and severe pain in the right shoulder ten minutes after the test.

This patient had five tubal insufflations and 23 diathermy treatments. She became pregnant four months after the last tubal insufflation and gave birth to a normal child (see Figs. 23, 24, 25, 26, and 27).

COMMENT

At the beginning of these treatments, the temperature of the vaginal electrodes was taken and found to reach from 106° to 108° F. After

A personal factor enters into all grading of carcinoma, and it must be remembered that more than one area of carcinoma should be studied, as the same tumor may show different grades in different areas. Thus, while the histologic type is an aid in forming a decision as to the method of treatment, other factors, as extent of the disease, technical operability, contraindication to surgery, etc., have to be considered.

DR. CHARLES A. BEHNEY.—Dr. Scheffey's observation that the danger of curettage is more than compensated for by the advantage of the information gained thereby, is in agreement with the opinions of most of us. I should like to call attention to a more dangerous procedure which has been recommended as a diagnostic aid; namely, the introduction of opaque substance under pressure into the uterus, suspected of being affected by carcinoma. At the Hospital of the University of Pennsylvania, there have been two cases of fundal carcinoma where after curettage, radium was inserted through a small cervical canal. After operation, in one instance, malignant curettings were discovered in a fallopian tube and in the culdesac in the second. Evidently the fragments had been "pumped" into the tubes by the piston-like action of the radium capsule. Before inserting radium into the uterus, one should be certain that the canal is well dilated beyond the dimensions of the tube.

The high percentage of patients in Scheffey's series with postmenopausal carcinoma and the relatively long period of bleeding before their seeking treatment as compared with the patients with premenopausal bleeding, again illustrates the fallacious impression of laymen and some physicians, that irregular bleeding at the time of the menopause can be temporized with.

While complete hysterectomy is the operation indicated for this disease, it must be remembered that in the most difficult cases complete removal cannot always be done with safety. These offer the worst prognosis and when included in any series may exaggerate the disadvantage of the supravaginal operation. Our experience at the Philadelphia General Hospital Tumor Clinic indicates that routine preliminary x-ray irradiation will render a greater proportion of our patients suitable for total hysterectomy than if this preparatory irradiation is omitted.

BROOKE M. ANSPACH.—At one time I thought the treatment of carcinoma of the fundus was a very simple matter. If a diagnostic curettage revealed a carcinoma of the fundus, a complete hysterectomy was to be performed forthwith. It was my impression that at least 75 per cent of the patients were cured. However, when statistics are analyzed, one finds how mistaken that idea is and what a low percentage there is of permanent recovery.

Diagnostic curettage is not always satisfactory to give a complete diagnosis. In Heymann's report of his treatment of cancer with radium, he points out that sometimes pathologists of equal distinction disagree in separating the benign from the malignant. Furthermore diagnostic curettage may not be done without some risk. In two patients coming under my observation, diagnostic curettage was followed by the development of carcinoma of the tibia, evidently metastatic. In the first I did a complete hysterectomy a few days after curettage and found that the carcinoma had advanced into the uterine wall almost to the serosa. The postoperative recovery was uneventful until the last hospital day when the patient complained of pain and tenderness in the shin.

In a second case during the last year, radium had been used elsewhere in small dose without diagnostic curettage. The symptoms continued. We did a gentle curettage and applied radium in full dose. The patient died three months later with carcinoma of the tibia.

While radium therapy in carcinoma of the fundus, either alone or in combination with x-ray, offers much and has proved its worth, the carefully considered objections that have been voiced by Sampson¹ are based on rational grounds, and the evidence presented is illustrative not only of the contraindications that may be encountered, but is probably explanatory of certain therapeutic failures. These objections may possibly be overcome in part at least, by more effective intrauterine radiation. Burnam,⁶ Bowing and Fricke,⁷ and Schmitz⁸ in this country, and more recently Heyman⁹ at Radinmhemmet have devised improved techniques that may aid materially in solving this phase of the problem. Continued improvement in the application of x-ray therapy likewise enters into the solution; theoretically ideal, it cannot always be employed to full advantage because of physical contraindications and intolerance to its effect.

7. Each patient with carcinoma of the fundus presents an individual problem in treatment, the management of which depends upon a thoughtful evaluation of all the factors concerned, and for which no "standardized" plan of therapy can be offered.

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MEDICAL TOWER, 255 SOUTH 17TH STREET
MEDICAL ARTS BUILDING, 16TH AND WALNUT STREETS

DISCUSSION

DR. F. SIDNEY DUNNE.—During the past year, in collaboration with Charles C. Norris, I reviewed the results of 211 cases of carcinoma of the fundus treated at the Hospital of the University of Pennsylvania. This series corresponded very closely with Dr. Scheffey's cases as regards age and symptoms.

With regard to the results of our treatment, the salvage was approximately the same in the group treated by hysterectomy as by irradiation, namely, 47.8 per cent and 43.8 per cent, respectively. It must be pointed out, however, that only 72.1 per cent of the hysterectomy patients were traced as compared with 92.1 per cent of the irradiated cases. Furthermore, in the group treated by hysterectomy the complete operation (panhysterectomy) yielded a salvage of 53.7 per cent compared with 34.3 per cent in the incomplete operation.

It is agreed that in the inoperable case, or in the patients in whom operation is technically difficult or contraindicated, irradiation alone is the treatment of choice. In the operable group, for those skilled in gynecologic surgery, operation offers the best chance for cure. However, statistics from some clinics tend to show that irradiation alone may give at least as good results as operation and is to be considered the method of choice if the patient is to be treated by one not skilled in gynecologic surgery. Healey, at the Memorial Hospital, advocates preliminary irradiation preceding panhysterectomy in the operable cases. The question of preliminary and postoperative irradiation is still controversial.

duced, data indicating how well this can be done are not available. The results of our analyses were as follows:

DATE OF SAMPLING	NITROGEN CONTENT IN GRAMS
4/24/36	13.216
5/ 7/36	13.500
5/21/36	13.622
6/ 3/36	13.875
6/ 4/36	13.501
6/18/36	13.328
7/ 2/36	13.573
Average	13.516 \pm 0.05
Coef. of Var.	1.4

This diet was, so far as could be judged from our present knowledge of dietetics, adequate in all respects. Principal sources of protein were milk, fish, pork, cereal, and peas. The subject's appetite was good and she never failed to eat the whole meal, but found the diet rather "filling" as pregnancy progressed.

The figures for the nitrogen utilization of the young woman whose study is the subject of this paper were compared with the averages, by months, of a large number

TABLE I. NITROGEN BALANCES DURING PREGNANCY

DAYS BEFORE DELIVERY	BODY WEIGHT KG.	FOOD NITROGEN GM.	URINE NITROGEN GM.	FECES NITROGEN GM.	NITROGEN BALANCE	APPARENT DIGESTIBILITY PER CENT
115	46.4	9.75	8.69	1.23	-0.17	88.4
101	49.5	13.52	9.12	1.52	1.93*	81.7†
88	51.8	13.52	9.21	2.61	1.84*	
86 to 72	51.9	11.82	8.76	1.75	1.31	88.9
71 to 61	52.3	11.70	8.70	1.44	1.56	86.6
60	53.6	13.52	9.24	2.67	1.81*	
46	54.5	13.52	9.05	†	2.00*	
32	56.8	13.52	7.54	3.33	3.51*	
18	57.7	13.52	6.91	2.22	4.14*	
5	56.9	8.47	6.38	1.65	0.44	80.5

*Computed by using the average digestibility of diet A.

†Average apparent digestibility for diet A.

‡It was not possible to obtain a feces sample because her physician had prescribed colloidal iron as a therapeutic measure. This also made it impossible to make other desirable fecal demarcations.

TABLE II. COMPARATIVE NITROGEN INTAKE AND RETENTION PER KILOGRAM BODY WEIGHT

DAYS BEFORE DELIVERY	FOOD NITROGEN INTAKE GM.	NITROGEN BALANCE GM.
115	126-102*	0.210 0.255*
101	101- 77	0.273 0.248
88		0.261 0.036
86-72		0.228 0.025
71-61	76- 52	0.224 0.030
60		0.252 0.034
46	51- 27	0.248 0.037
32		0.238 0.062
18	26- 1	0.234 0.072
5		0.149 0.008
Average		0.232 0.034

*Data in these columns arranged from the continuous metabolism study of Hummel, Sternberger, Hunscher and Macy.¹

Sometimes it might prove better in a case in which the condition bears all the earmarks of a carcinoma to do a hysterectomy without a preliminary curettage, but, of course, we must face the fact that we may remove the uterus needlessly in poor operative risks.

DR. SCHEFFEY (closing).—Several of these patients were treated by supravaginal hysterectomy either by oversight or necessity. Two of the survivors, exhibiting low-grade malignancies, were treated in this manner. The complete operation had been planned, but extensive induration of the broad ligaments made it impossible to do so in one instance. These patients received x-ray postoperatively and remain in the salvaged group.

I do not wish to give the impression that prognosis depends on the cell type alone. It is merely one factor. I agree that such varied pathology may appear in one slide, that a single piece of tissue may not be sufficient to establish gradation, and that several should be examined.

In this series we have shown clearly that the advantages of the curette far outweigh the objections which have been raised by some. Each case is an individual problem and the treatment, therefore, must be based on the consideration of all factors concerned.

THE NITROGEN BALANCE OF A YOUNG PRIMIPARA*

WALTER H. SEEGER, PH.D., YELLOW SPRINGS, OHIO

(From the Samuel S. Fels Research Institute, Antioch College)

THE protein requirements during pregnancy are probably more clearly defined, on the basis of data available, than those of any other dietary constituent; it is possible to study the metabolism of any one individual and compare the result with an abundance of figures in the literature. Since little is known about the metabolism of comparatively young individuals during pregnancy, it seemed desirable to study such a case when it was available. The primipara whose nitrogen balance was studied during the last trimester of pregnancy was fifteen years and twenty-five days old when she was delivered of a healthy female child weighing 7 pounds.

The metabolism periods were three days in length, and, although the first two days were considered preliminary, the urine was analyzed each day. The feces was marked with carbon and earmine, and Kjeldahl analyses were made on wet samples. She ate one diet (diet A) for seven three-day periods at two-week intervals. Two other diets were also eaten on three-day metabolism periods, and in addition daily food and urinalyses were made for twenty-one consecutive days (see Fig. 1 for distribution of metabolism periods), during which time the diet was variable and self-chosen. Fecal analyses for this last mentioned period were done on pooled excretions.

The subject lived at Fels House and was constantly under observation when dietary studies were in progress. Her food was prepared and carefully weighed for her and a quantity representing half the amount she ate was dried at low temperatures, ground fine in a mortar and analyzed. Diet A was repeatedly analyzed for the purpose of learning how well the nitrogen content of a mixed human diet can be reproduced. Though this matter of diet constancy is of importance in judging the validity of conclusions in any experiment in which a given diet must be repro-

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as a source of protein.* There were similar but less marked differences between the utilization of the self-chosen food on the one hundred and eighteenth and seventh days before delivery. Both of these last diets contained protein of good quality, but it was apparently eaten in insufficient quantity to permit optimum storage.

Although higher retentions have been found to be associated with high nitrogen intakes it is apparent from the utilization of diet A that the quantity retained by this person was more a function of time in pregnancy than of quantity ingested.† The gravid individual will, by a shift from the exogenous phase of metabolism to the growth of the fetus, store more of the nitrogen in a given diet when it is most needed if that diet is adequate to furnish the required nitrogen and energy.

Daily urinalyses were made during the three-day metabolism periods for the purpose of gaining information on the question of urine nitrogen "lag." In order to avoid a distaste for the diet, and for other practical reasons, it was desirable to have the metabolism periods of minimum length. With two exceptions, the quantity excreted on the third day compared favorably with the excretion on the second day. This fact suggests that, from the standpoint of urine nitrogen lag, one may obtain significant balance data in short metabolism periods when there is little difference between the plane of nutrition during the experimental period and that of the non-experimental period. This confirms and amplifies the unpublished data of Potgeiter and Pyle who have repeatedly used short observation periods in their metabolism studies in this laboratory.

When the subject was on the variable self-chosen diet, there was no correlation ($r = 0.04$) between food nitrogen intake and the nitrogen excreted in the urine on the same day. The lack of relationship between these two variables is also evident in Fig. 1. It must be realized that in this instance, in contrast to the three-day controlled periods, the quality of the protein has an important rôle.

SUMMARY

A fourteen-year-old human subject stored approximately the same quantity of nitrogen in the last trimester of pregnancy as older individuals do. Although her diet was the same (13.516 gm. nitrogen, or 84.5 gm. protein) for seven three-day metabolism periods, she stored more of the nitrogen in that diet toward the end of pregnancy.

Under experimental conditions the nitrogen content of a mixed human diet can be kept constant to within a coefficient of variation of 1.4.

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*From clinical tests it is known that this subject was anemic. Bethell³ has emphasized that a high intake of protein of good quality is an important factor in the treatment of the anemia of pregnancy. Since this diet was eaten for only a comparatively short time one could hardly expect it to alleviate her condition.

†A few pregnant rats were fed a fixed quantity of an adequate ration daily and the quantity of urine nitrogen determined on forty-eight-hour collections. All but one refused food toward the end of pregnancy. The one successful experiment definitely showed the progressive increase in storage toward the termination of pregnancy. Although the dietary factors were equally conducive to storage at all times, the time in pregnancy was ultimately the determining factor in the quantity of nitrogen stored.

of subjects previously studied in various laboratories. They were also compared with the work of Hummel, Sternberger, Hunseher and Macy¹ who studied a subject continuously during the last trimester of pregnancy.

Hunseher² and her associates have made a compilation of figures for the average retentions distributed from the third to the tenth month in 945 individual balances made on patients of various ages and on all sorts of diets in various stages of pregnancy. The means per month were 2.84, -0.15, 1.99, 2.59, 2.18, 3.23, and 3.46 gm. of nitrogen daily. While there were variations in retention on different levels of intake, negative balances predominated with intakes below 10 gm., and only positive balances were noted when the intakes were above 18 gm. per day. When these trends are compared with the results given in Table I, it is evident that the quantity of nitrogen retained by this young subject was not different from the average retained by this mixed group of individuals with their varying food intakes.

Hummel, Sternberger, Hunseher and Macy¹ made a detailed study of a woman when she was thirty-seven years old and in her fourth pregnancy. Their subject was under continuous observation during the last trimester of pregnancy and also

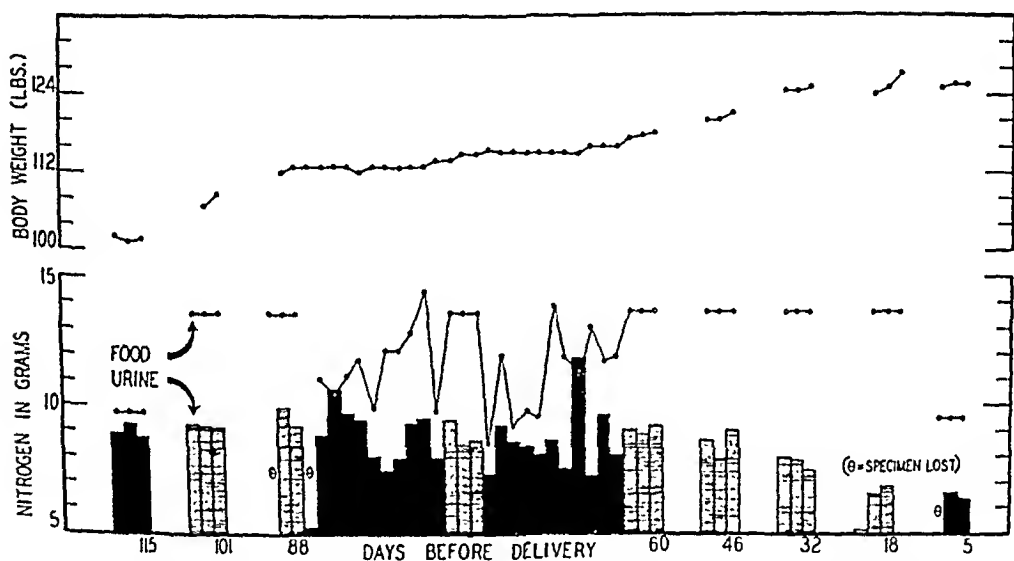


Fig. 1.—The chart shows the daily urine nitrogen excretion, food nitrogen intake and gain in body weight in the last trimester of pregnancy. The spaces between histograms merely serve to indicate that no observations were made, and have no absolute time value. The hatched histograms represent diet A.

during the lactation period. She weighed 78.5 kg. just before parturition and ate on the average of 19 gm. of protein nitrogen daily during pregnancy. Since she was heavier and consumed more protein than our subject, the comparative figures given in Table II are in terms of protein intake and retention per kg. body weight. The data of Hummel and others have been arranged in twenty-five-day averages. The figures compare as favorably as can be expected in a metabolism study of this kind, and show that the metabolism of the young individual is similar to that of the adult.

It can be seen that there was an improvement in the nitrogen balance, on diet A, with the advancement of pregnancy. If it is assumed that the digestibility of this diet was always the same, and that the somewhat variable digestibility figures are to a considerable degree due to unavoidable errors in the demarcation of the twenty-four-hour excretions, this improvement is commensurate with a decrease in urine nitrogen excretion (Fig. 1). Apparently some of the protein of this diet which is used for storage late in pregnancy is excreted as the end-product of exogenous metabolism during the period when the requirements for fetal growth are not so large. This change in the utilization of the diet is evidence that it was adequate

urine negative. X-ray was suggested at this time to determine the presence of a monstrosity or multiplicity. This was refused. Thereafter, there was no further increase in weight. On October 5, at her last antepartum visit her weight was 163 pounds. Blood pressure 114/60, urine negative. Edema had not entirely subsided, hydramnion had not increased in size. Fetal heart heard in L.L.Q.; fetal parts could not be definitely made out.

Labor commenced on October 5 at term at 7 P.M. and patient was admitted to the hospital two hours later when the following was noted: Pains every two minutes, fetal heart L.L.Q., position L.O.A., membranes intact, cervix effaced, three fingers' dilated. Rectally: presenting part cephalic and engaged. Fully dilated at 9:20 P.M. Membranes ruptured and spontaneous delivery of normal female infant at 9:30 P.M. in L.O.A. position. There was a moderate amount of amniotic fluid. A few minutes later another amniotic sac appeared at the vulva, which was punctured and a profuse amount of a bloodstained fluid escaped. A

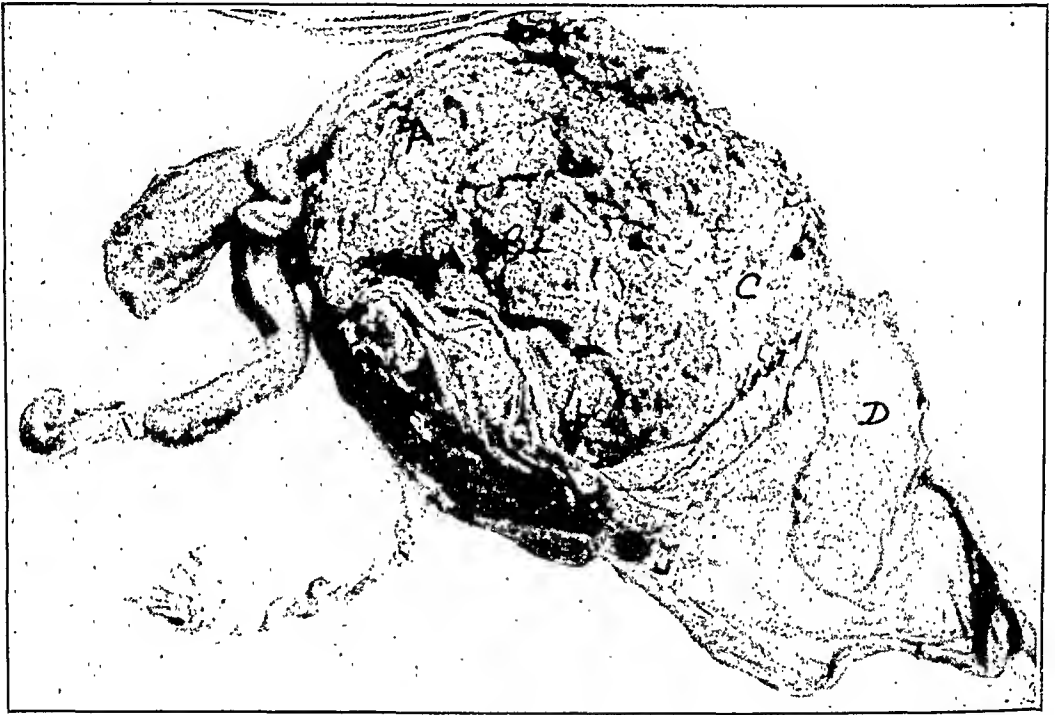


Fig. 1.

macerated fetus was extracted which presented by footling. The placenta was delivered intact. The uterus being atonic, was not firmly contracted with a resultant slow but steady blood loss. Uterus and vagina tightly packed. The shock was very profound with an imperceptible pulse and zero blood pressure readings for thirty-six hours postdelivery. During this time two transfusions of whole blood were given, 1,000 c.c. and 750 c.c. followed by a continuous venoclysis of 5 per cent glucose in saline. Oxytocics, together with the other known methods of shock treatment were instituted. Patient was discharged from the hospital on the tenth day postdelivery.

The temperature rose to 103.5° F. the first day postpartum and receded to normal on the sixth day. On discharge the uterus was well involuted. Blood pressure 114/80, pulse 90, temperature 99° F. Blood count: Hg 51 per cent, R.B.C. 2,500,000, W.B.C. 12,000; 68 per cent polymorphonuclear leucocytes, 32 per cent lymphocytes, 1 per cent eosinophiles. Urine negative.

The placenta (Fig. 1) weighed 550 gm. and measured 18.5 cm. in diameter and 2.5 cm. in thickness. It was divided into three distinct segments. An outer necrotic

TRIPLET PREGNANCY WITH PAPYRACEOUS FETUS

SAMUEL L. SIEGLER, M.D., F.A.C.S., BROOKLYN, N. Y.

TRIPLET pregnancy is not a common occurrence. At the Brooklyn Woman's Hospital, this was the first case of triplets in over 14,000 births. By no means do all triplets survive birth and infancy.

The incidence in triplet pregnancy of the delivery at term of a live normal child, together with a macerated fetus, apparently of seven and one-half months' gestation and a mummified or papyraceous fetus approximately of eight or nine weeks' gestation, is relatively rare.

Beierlein collected 20 cases from the available literature in which there were reported triplet pregnancy with twin papyraceous fetuses. He also quotes Bertog and Maryanchik who describe triplet pregnancies with single papyraceous fetuses. Von Erlach and Sunger mention similar cases. Bretschneider observed a papyraceous fetus accompanying a premature infant and an acardiacus. Two examples of the birth of triplets, one living and the other two macerated, have been reported, one by Perdu and the other by Doesschate.

REPORT OF CASE

Mrs. E. F., aged thirty-five, para i, gravida iii, was first seen by me for this pregnancy on March 11, 1936. Past history: Hyperthyroidism in 1934 and 1935. Was treated medically with apparent good results. Still complaining of palpitation occasionally, but kept a steady weight of about 140 pounds. Basal metabolism plus 8. Hemorrhoidectomy June, 1934. Menses started at fourteen years, recurred every twenty-four days, and she bled for about five days with some clots which was usually followed by a blackish discharge for ten days thereafter. Married eight years, one spontaneous delivery in 1930, one spontaneous abortion in 1935 of a six-weeks' old gestation for which she was curetted and with no sequelae following. Last menstrual period Jan. 8, 1936. Expected date of confinement October 15.

On April 30, 7 weeks after the last menstrual period patient started to bleed which was accompanied by small clots, cramps and a chill. (She attributed this to a severe attack of sneezing.) This bleeding persisted for four days. Following this she stained for ten days, with the resultant "muddy" discharge until May 23, when she bled again for three days; this time not as profuse as heretofore, and with no clots. Rectal examination at this time showed the uterus to be enlarged to about a ten weeks' gravidity and the cervical os closed. Two units of Progestin were administered on April 30 and on May 1. The cramps subsided. Thereafter one-half unit was administered daily for the next five days, then every other day until the twenty-sixth of May. There was no further bleeding or cramps. Fetal life was felt at the fifth month.

Pregnancy continued normally until about the middle of the seventh month of gestation when patient complained of a sudden swelling of the face, hands, ankles, and an enlargement of the abdomen. Shortness of breath and palpitation were also noticed. Examinations at this time showed an edema of the parts noted together with a polyhydramnion. Only one fetal heart heard in L.L.Q. Fetus in the L.O.A. position and cephalic presentation. The vulva was considerably edematous. There was an increase in two weeks of $9\frac{3}{4}$ pounds in weight from her previous visit, from $154\frac{1}{4}$ pounds to 164 pounds. Blood pressure rose from 120/70 to 130/80;

obstaele and has to be removed. More serious complications may arise if a papyraceous fetus is retained, because this may cause hemorrhages or infections during the puerperium. Its diagnosis is almost impossible unless a roentgen ray accidentally discloses the anomaly. All other symptoms which might reveal it are uncertain.

The causes of the formation of a papyraceous fetus are unknown. Many theories have been advanced. Wolff mentions disturbance of the placental circulations with predominance of the heart of one of the fetuses. Syphilis, nephritis, amniotic bridges

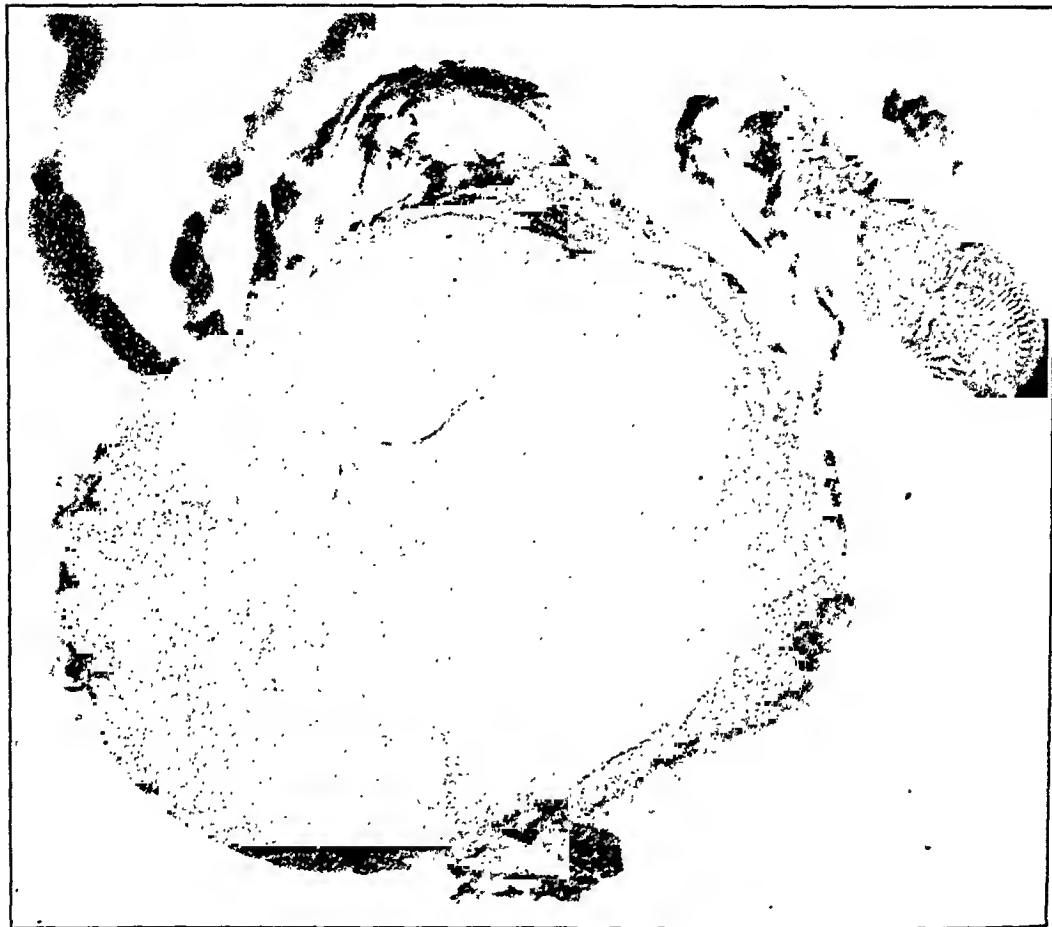


Fig. 2.

stricturing one of the umbilical cords, mechanical injuries, endometritis, etc., have been mentioned as causes. None of them was present in this case.

I wish to thank Dr. Max Dannenberg for his roentgenogram interpretations and Dr. Max Goldzieher for his microscopic pathological findings.

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surface (Fig. 1, *A*) measuring 14 cm. by 5 cm. contained many small white infarcts with a velamentous insertion of the cord. The cord measured 30 cm., was necrotic, slimy, and edematous. To this was attached the macerated fetus which weighed 730 gm. and was 25 cm. long. The center portion (Fig. 1, *B*) was 15 cm. by 12 cm. from which the outer necrotic area was separated by a distinct ridge, evidently the site of fusion of the two lobes, was normal in its appearance and consistency. The cord was centrally attached and measured 31 cm. The normal living infant weighing 2,107 gm. was 36.4 cm. long. There was a whitish, hard, fibrotic area at the other end of the placenta (Fig. 1, *C*) measuring about 3 cm. by 10 cm. from which the normal portion was sharply demarcated. Separating the layers of amnion at this end, one felt a small leathery hard mass (Fig. 1, *D*) measuring 6.3 cm. in length and 3.5 cm. in width. There was no fluid in this sac, the mass being a mummified or papyraceous fetus. Its cord, of threadlike caliber and measuring 6 cm. in length, could be seen entering the placental site at the outer edge of this fibrotic portion.

Microscopically: Extensive necrosis of the placenta comparable in appearance to an infarction. Other areas in the placenta showed scattered small foci of coagulation necrosis. Deposits of calcium were found both in the necrotic areas and also in the apparently viable villi.

There were two distinct choria and three amniotic sacs, the one chorion and its sac containing the macerated fetus, and the other chorion with its two sacs, one containing the living fetus and the other the papyraceous fetus.

DISCUSSION

From the description of the placenta herein presented, this was a case of biovular triplets, since there were two distinct choria and each of the fetuses developing in its own amnion. Still one can only tell if one is dealing with uniovular, biovular, or triovular triplets if the three were alive. Bushke states that this can only be proved by determining if they are concordant or discordant, in that there be a similarity or identity with regard to a particular phenotypic characteristic among individuals under discussion showing a definite characteristic. This, however, one could not tell in this case.

The period of development of the macerated and the papyraceous fetuses can possibly be determined in this case:

(a) By the history of bleeding in the early weeks of gestation, when in all probabilities there was an arrest in the development of one of the fetuses with the resultant mummified fetus. It is quite possible that we would have had in all likelihood an abortion of all of the nidations, were it not for the administration of the corpus luteum extract. This clinical entity should actually have been termed a missed abortion. The death of the macerated fetus occurred at about seven and one-half months of gestation, for it was at this time that the patient experienced a sudden gain of weight with the associated manifestations of hydramnion, edema, and no further gain in weight thereafter.

(b) By the roentgenograms which showed the stage of ossification of their skeletons.

In the macerated fetus there was an absence of the epiphysis of the distal ends of the femora which should be present at birth, hence placing its development at about the eighth month. In the papyraceous fetus there were noted ossifications of the ilia, scapula, long bones and the tiny centers of the phalanges with absence of the superior ramus of the ischii, placing its arrest of development at about the eighth week (Fig. 2).

However, the presence of a papyraceous fetus is certainly often overlooked, because the placenta is not always so accurately examined. Its presence is rarely of clinical importance. Sometimes a papyraceous fetus lying at the os uteri forms an

the first six cases, vaginal temperatures were no longer taken because in practically all six cases when the current was raised to 2,500 milliamperes the temperature in the vaginal electrodes remained between 106° and 108° F.

In two of the patients in this series I used the abdominal-sacral electrodes because they both followed postpartum infection.

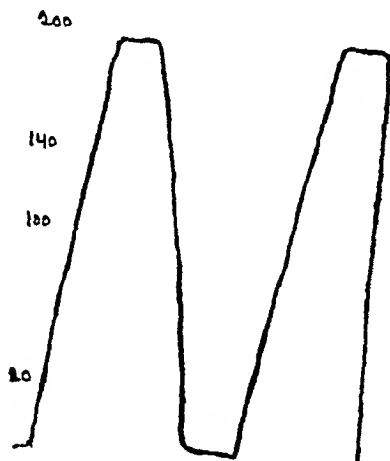


Fig. 19.

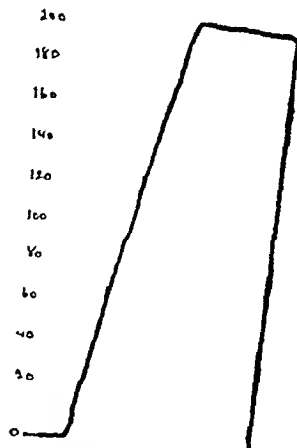


Fig. 20.

Fig. 19.—Case 5. First Rubin Test: The pressure rose twice to 200 mm. of mercury; there was practically no pain during the test.

Fig. 20.—Case 5. Second Rubin Test: After eight diathermy treatments the pressure rose to 200 mm. of mercury and was maintained for three-quarters of a minute, then allowed to drop. There was no pain during the test.

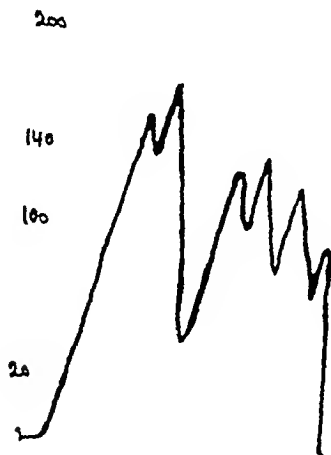


Fig. 21.

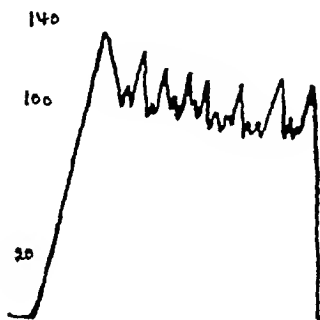


Fig. 22.

Fig. 21.—Case 5. Third Rubin Test: After twenty-four diathermy treatments the pressure rose to 160 mm. and dropped to 140 mm. and then rose again to 180 mm. and dropped to about 50 mm., rising again to about 130 mm., fluctuating between 70 and 130 mm. There was no pain during the test and no shoulder pains when sitting up.

Fig. 22.—Case 5. Fourth Rubin Test: After thirty-six diathermy treatments the pressure rose to 140 mm. of mercury, dropped to 100 mm. and then fluctuated between 90 mm. and 120 mm. with very good normal tubal contractions. The patient had no pain during or after the test. Appropriate tests showed that this patient was hypersensitive to pain.

The combined treatment of diathermy and tubal insufflation may produce a favorable result in patients in whom the tubes are the seat of extensive strictures, agglutinations, and adhesions which can be overcome by a pressure of approximately 200 mm. of mercury.

PHOTOGRAPHIC RECORDS OF THE CERVIX UTERI

J. M. BRUNER, M.D., L. E. ROSEBROOK, M.D., AND G. W. CUSHMAN, B.A.,
DES MOINES, IOWA

PHOTOGRAPHS of the cervix uteri are of value as permanent records of the cervix before and after such procedures as cauterization, radium application, and plastic operations. There are no good photographs of the cervix in medical textbooks or publications due to certain inherent difficulties in photography. The cervix is generally illustrated by drawings which are often inaccurate and do not present the true conditions. For these reasons an attempt was made to work out a simple technique of making good photographic records of this organ.

The two chief difficulties in photography of the cervix are proper illumination and adequate exposure. The ordinary bivalve vaginal speculum does not give satisfactory exposure. In many patients the vaginal walls are quite redundant and although the anterior and posterior walls are well retracted by the two blades of the speculum, the lateral walls fall together almost obscuring the cervix. Another difficulty is the great variation in the depth of the vagina. The direction which the cervix points, due to the position of the uterus, is also important; the cervix must be brought into a favorable position for photography.

The greatest problem, however, is illumination. It is easy to light the cervix by means of strong floodlights or mirrors outside the speculum, but photographs taken with such lighting are flat and have no detail, because the light rays are parallel to the photographic plane. The light must come from an angle, so that some degree of modeling will be produced, and the resulting photograph will possess third dimensional qualities.

For this purpose a special tubular speculum was constructed with lights incorporated within the speculum. After considerable experimentation the length selected was five inches. This was found to be long enough to expose the cervix in the deepest vagina, and in patients with a very short vagina the instrument would not protrude outside to any extent. When once introduced with the obturator in place, there was very little tendency for the speculum to be forced out of the vagina except by unusual straining. Such a speculum provides a perfectly clear round field with no interference laterally from the vaginal walls or vulva.

The cervix is engaged by the distal end of the speculum which has a $\frac{3}{4}$ inch bevel (similar to the Ferguson type of vaginal speculum). By means of the beveled end almost any cervix, no matter in what direction it points due to uterine position, can be brought into proper position for photography. Two sizes of tubular speculum were made, one $1\frac{1}{2}$ inches in diameter which could be used in almost any married woman, and a larger size—2 inches in diameter which was easily introduced in women who had borne several children. This gave an excellent large field, and would accommodate the largest cervix which was encountered.

The light is furnished by two radio dial bulbs which give a brilliant light and are cheaply replaced. These are eccentrically placed on one side of the speculum, with a light shield, leaving ample room for photography. The optimum distance for the lights was found to be 4 inches; a light placed closer than this caused too deep a shadow on the opposite side of the cervix in which no detail was visible.

The secret of success for good photography of the cervix is twofold: first, the cervix itself must be deflected somewhat to one side and this is accomplished by means of the beveled tubular speculum; second, the light must be thrown on the

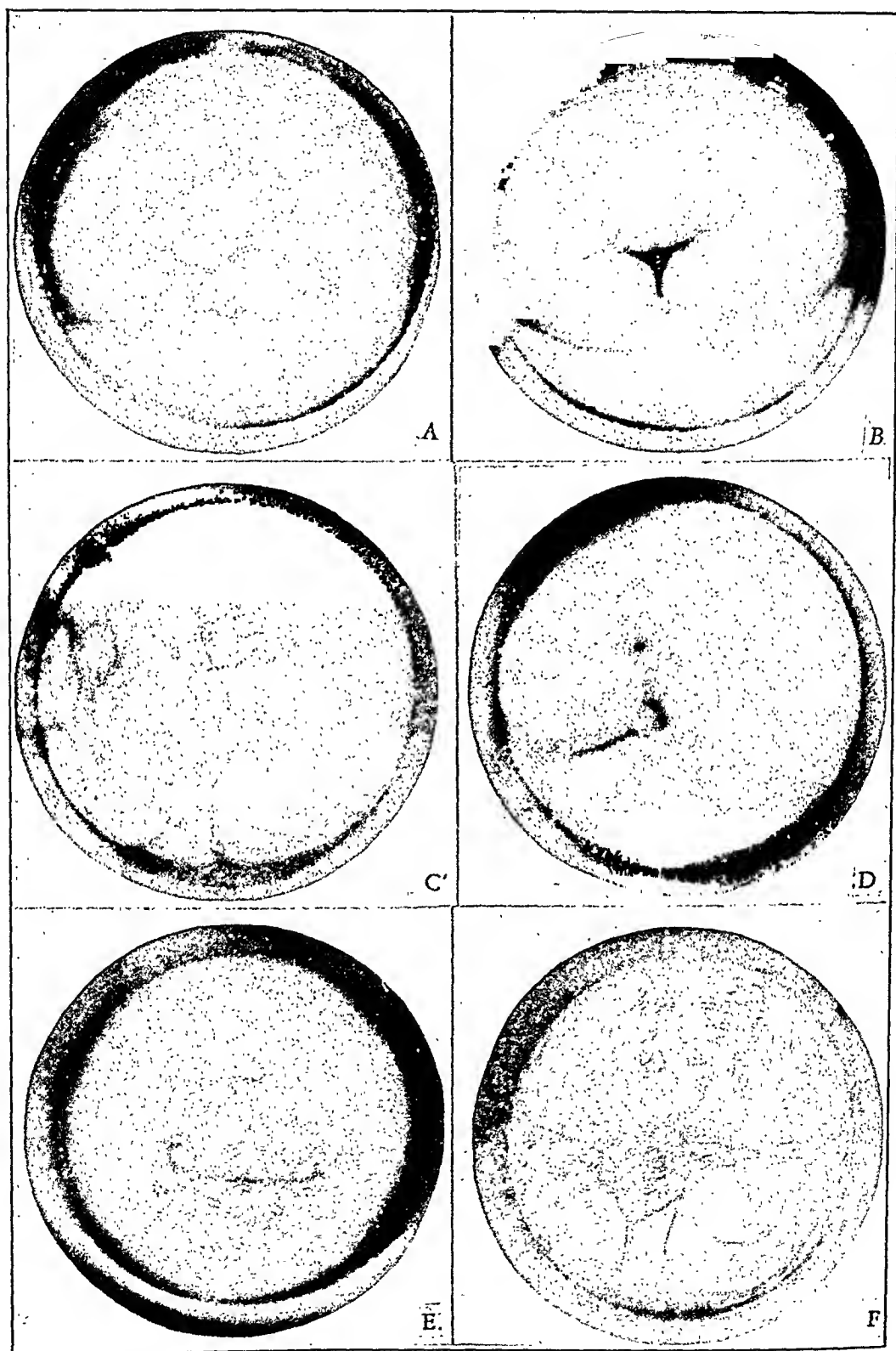


Fig. 1.—Speculum, obturator and light carrier for photography of the cervix uteri.

cervix from the quadrant opposite that to which the cervix has been deflected. For instance, the best position for the cervix is first ascertained by rotating the beveled speculum. If the cervix points posteriorly, the light carrier is rotated until the lights are in an anterior position. This provides the maximum amount of shadow effect producing black and white contrast in the photograph, and an impression of depth.

With the speculum shown here it is easy to obtain good photographs of the cervix. The patient lies on an examining table, preferably a cystoscopic table, with knee crutches. The bladder and rectum should be empty. The lubricated speculum is now introduced with the obturator in place. If necessary the gloved left hand is used to depress the perineum.

The obturator is now removed and any excess mucus or discharge removed with a few moist cotton balls. It is not advisable to attempt to remove mucus with such digestants as caroid. Any attempt to cleanse the cervix too thoroughly is likely to start bleeding.

The current, supplied by a battery of dry cells, is now turned up and the most favorable lighting of the cervix is obtained by rotating first the speculum, then the

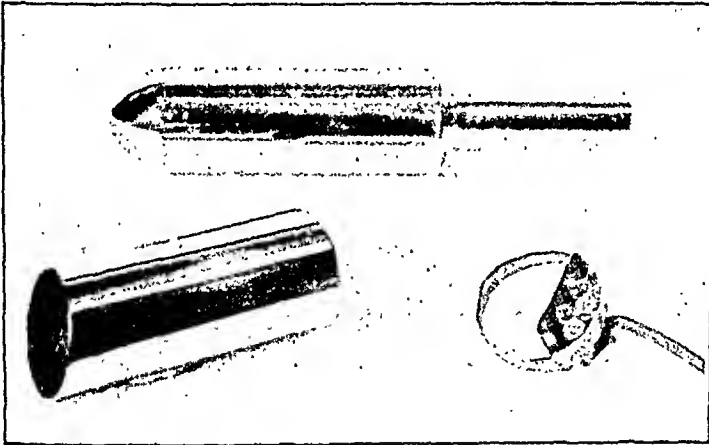


Fig. 2.—Photographs of the cervix uteri made with the equipment described. *A*, Old stellate laceration of the cervix. *B*, The same cervix six weeks after cauterization. *C*, Chancre of the lateral vaginal fornix. Positive dark-field. (Cervix pushed aside.) *D*, The same cervix eight weeks after antisyphilitic therapy. Chancre reduced to scar. *E*, Eroded cervix with nabothian cysts. *F*, Vaginal vault after vaginal hysterectomy. Granulation tissue at site of closure.

light carrier. A Leica camera on tripod is set up in front of the table, and camera lens and speculum are brought into apposition. An adjustable table is of great help in raising or lowering the hips of the patient. The camera is placed at a maximum distance from the speculum (8 to 10 inches) in order to secure the greatest possible depth of focus. The ground glass attachment for the Leica accurately defines the field and insures accurate focus. A small piece of paper with printed matter may be placed on the cervix to aid in focusing.

The patient is instructed to hold her breath at the end of expiration. (Holding the breath at the end of inspiration may force the cervix downward thus getting the subject completely out of focus.) Using Eastman "background film," the length of exposure will not be over three to five seconds. It is very unusual to have any difficulty due to movement of the patient, and very few patients complain of any sort of discomfort. Using the above method it is possible for the gynecologist to obtain good photographic records of the cervix in a few minutes' time and without undue trouble.

ABDOMINAL PREGNANCY NEAR TERM, OPERATION AND HORMONAL STUDIES OF THE BLOOD AND URINE WITH THE PLACENTA LEFT IN SITU*

ARTHUR S. MACGREGOR, M.D., BROOKLYN, N. Y.

THE patient, who was thirty-four years of age and of Italian extraction, was admitted to the Norwegian Hospital on Nov. 18, 1935. Her physician had advised hospital care because of the severity of nausea, vomiting, constipation, and painfulness of fetal movements.

Her past history aside from her menstrual, marital, and obstetric history was irrelevant. Her menses began at thirteen, occurred regularly at twenty-eight-day intervals and were of four-days duration, being associated with moderate dysmenorrhea. She had first married in 1919 and two pregnancies occurring shortly thereafter were terminated by induced abortions at three months and apparently were not followed by sepsis. After living with this husband for two years she divorced him and remarried in 1924. She did not conceive again until 1929 at which time a left salpingectomy was performed for a ruptured ectopic gestation. There were no pregnancies from then on until the one under consideration.

The last menstrual period began on March 15, 1935 at the expected date and was normal in all respects. About four weeks later she began to spot and experienced cramplike pain such as she would have during her periods. This spotting and pain continued for the next two weeks, the bleeding on one occasion amounting to a definite flow for several hours. There was no further bleeding during the remainder of the pregnancy. Pain along the entire right side of the abdomen and chest was present at intervals associated with attacks of weakness. The pain was often relieved by enemas. Nausea and vomiting were a prominent symptom throughout, the patient losing eighteen pounds in weight. Constipation was a persistent symptom also. In the last trimester the fetal movements caused the patient great distress in the upper abdomen.

I first saw her in consultation on November 27, three and one-half weeks prior to her estimated date of confinement. The patient was found to be a poorly nourished individual with a diminished hemie component, who did not appear well. Her temperature was 98.2° F., pulse 85, respirations 20, and blood pressure 116/76. Physical examination revealed no abnormalities aside from evidences of weight loss, the breast signs of pregnancy and the abdominal findings.

The abdomen was greatly enlarged as though by a twin pregnancy. What first appeared to be the fundus uteri was found to be 27 cm. above the symphysis, and there seemed to be a marked widening of the upper portion of the abdomen. Palpation revealed, however, that the child was in the upper abdomen lying transversely with the head on the left side just beneath the costal margin. The fetal parts were unduly prominent. The right lower quadrant of the abdomen was occupied by a semisolid fixed mass with a rounded upper edge which extended upward to slightly above the umbilicus and appeared to arise from the pelvis. This mass seemed to fuse with another mass which was also present in the lower abdomen to the left of the first mass extending over into but not completely filling the left lower quadrant and rising to the level of the umbilicus. The fetal heart was heard in the upper left quadrant. On vaginal examination the cervix was found high up

*Presented at a meeting of the Brooklyn Gynecological Society, April 2, 1937.

on the left side of the pelvis. The right fornix was filled by a rounded semicystic mass of large size which was continuous with the masses felt abdominally. The cervix was soft but not patulous or effaced. An x-ray examination made at eight months revealed that the child was lying directly transverse in the upper abdomen with the head on the left side. The child did not seem enclosed by a shadow such as it would be were it intrauterine. The grotesque sprawled out positions of the extremities are not seen in uterine pregnancies. R. B. C. 3,500,000; Hb 69 per cent. The white cell count was 7,500 with 80 per cent polys. The urine was negative except for a trace of albumin. The blood chemistry report was nonprotein nitrogen 28.7 mg., urea nitrogen 11.3 and glucose 89 mg. Operation was decided upon a week later because of the patient's suffering, and because it was felt that the baby was large enough to be viable.

On December 3 abdominal section was done under ether anesthesia. At this time the patient was about two and one-half weeks from term. An incision was made over the right rectus muscle about an inch to the right of the umbilicus, one-third of the incision being above and two-thirds below the umbilicus. The rectus muscle was retracted outward and the peritoneum incised. The omentum was found to be adherent to the anterior abdominal wall throughout the lower half of the incision. These adhesions were cut and the bleeding points in the omentum ligated. The omentum was drawn up and the pelvis explored. The uterus was found to be soft and enlarged to the size of a five to six months' gestation. It was pushed to the left by a mass about 25 by 10 by 10 cm. in size. This proved to be the placenta which was attached to the posterior surface of the right broad ligament extending downward into the culdesac and outward to the lateral pelvic wall. Fine adhesions between the appendix, cecum, small intestine and the maternal surface of the placenta had to be freed before the full extent of the placental attachment could be determined. The cord was found to emerge from deep in the pelvis and the placental site extended from the culdesac up over the pelvic brim. There was no evidence of the membranes except over the maternal surface of the placenta and no fluid was present in the abdomen. The right tube could be traced for a distance of about four inches when it seemed to fuse into the placental mass. It was flattened and about one-half inch in width. The child was found to be lying transversely in the upper abdomen beneath the omentum, transverse colon, and stomach. It was extracted by the feet and breathed immediately. The child was found to have a calcaneus deformity of the right foot and asymmetry of the head, thorax, and abdomen of a moderate degree. The birth weight was 2,660 gm. The cord was cut and ligated close to the placenta. No attempt was made to separate the placenta from its attachment. The abdomen was closed in layers without drainage.

The patient had an extremely mild postoperative febrile reaction. There was practically no abdominal distention at any time nor was there any vomiting. On the twelfth day a few drops of serum were evacuated from the incision which otherwise healed by first intention. The patient was kept in bed until the twelfth postoperative day and was discharged on the nineteenth day. At the time of discharge the placental mass filled the right lower quadrant of the abdomen extending upward to the level of the umbilicus. The uterus was undergoing moderately rapid involution, being the size of a five to six months' gestation at the time of operation and nineteen days later but little more than half that size. During her hospital stay there was no uterine bleeding noted. On the fourth and fifth days the breasts which had remained flaccid, were pumped to stimulate lactation. There was no milk secretion present and the breasts never showed any signs of engorgement during her hospital stay or subsequently. On January 8, thirty-five days after the operation, slight spotting occurred and persisted for three weeks. The patient had a month of amenorrhea and since then has menstruated every twenty-four to twenty-seven days, having moderate dysmenorrhea similar to what she previously

had. Eight weeks postoperatively the placental mass had diminished but slightly in size but the uterus had almost returned to normal size. Examination sixteen months after the operation still revealed the presence of the mass in the right side of the pelvis. It was about the size of a large orange and was found to be partially fixed to the side of the pelvis. The uterus was normal in size and partially mobile. The patient stated that never at any time since leaving the hospital had she had any discomfort. The baby has had the calcaneus deformity corrected and aside from slight asymmetry of the head appears normal in all respects.

It was felt that it would be interesting to make a survey of the hormone content of the blood and urine in this case. Through the kindness of Drs. Frank and Goldberger this was done at the Mt. Sinai Hospital.

The blood taken on the second day following operation gave a full estrogenic reaction in 40 c.c. of blood as in normal pregnancy. A week later on the ninth day the reaction was negative in this quantity of blood. The first urine on the second day gave a positive Friedman test with 0.75 c.c. of urine which corresponds to 1,333 rabbit units per liter. On the fifth day the urine showed only 50 rabbit units per liter while subsequent Friedman tests were negative on the tenth, seventeenth, and twenty-fourth postoperative days. It was determined that the estrogenic reaction in 40 c.c. of blood became negative between the second and ninth days and that the prolactin titer in the urine diminished rapidly, becoming insufficient to produce a positive Friedman test on the tenth day. From these studies it would appear that the placenta ceased producing prolactin and estrin in appreciable amounts within less than ten days after the operation.

Ware and Main¹ reported a very similar case of abdominal pregnancy in which the placenta was not removed. Nineteen Friedman tests done during the first thirty-five days after the operation were all positive, the first negative being obtained on the thirty-sixth day. Three others done shortly thereafter were also negative. Halban in 1905² was the first to note that lactation was inhibited by the retention of the placenta and that it occurred usually about three days after the removal of the placenta. Frank³ describes a case in which the placenta was retained in utero for fourteen days with lactation following its removal in three days. Riddle⁴ isolated the hormone prolactin from the anterior lobe of the pituitary in 1932. The weight of experimental evidence today makes it appear that estrin and possibly progesterin prepare the breasts for lactation and that prolactin may be the activator of or, at least, is responsible for the continuance of lactation.

Estrin has been found to inhibit lactation as has to a lesser extent the anterior pituitary-like substance. The occurrence of lactation has been attributed to the removal of these two hormones from the blood circulation. In the case reported it would appear that these two hormones disappeared rather quickly from the maternal system and yet lactation did not occur. I can offer but two explanations for this. One, that this patient's anterior pituitary gland may have been deficient in prolactin production or second that in cases of retained placenta some factor other than the continued production of estrin and prolactin inhibits the action or production of prolactin.

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ACTINOMYCOSIS OF THE OVARY*

FREDERICK H. FALLS, M.D., CHICAGO, ILL.

(From the Department of Obstetrics and Gynecology, University of Illinois, College of Medicine, and the Gynecological Service, Cook County Hospital)

ACTINOMYCOSIS of the ovary is a relatively rare disease. Haselhorst up to 1928 collected 60 cases. Only three primary ovarian cases have been reported. The cases are usually secondary to bowel, lung, or head and neck infections.

None of the patients in the 60 cases reported by Haselhorst recovered permanently. Schugt reported an unusual case of a patient in 1930 who had an infected abortion four years previously with slow recovery. She developed a tender mass in the region of the right ovary which was drained vaginally and was then treated by x-ray. About twelve weeks later the left tube and ovary became involved in a similar process and was drained in the same manner. This was followed by x-ray therapy and the patient was well one year later at the time of the report.

Most of the reported cases have been noted in the right ovary, although the left ovary may become secondarily infected. It is probably very rare that infection spreads from the uterus, cervix, or tube to the ovary, although the possibility cannot be denied. The spread from the gastrointestinal tract is much more probable, and according to more recent investigators, may be associated with the fact that these organisms have been found in the human mouth around carious teeth.

The probability that the organisms occur in grasses and grains is remote, since the organism does not form spores and is not resistant to heat, cold, or drying.

Pathologically, the organism produces a granulomatous change in the ovarian tissue which eventually breaks down to form pus containing the characteristic sulphur granules. The condition cannot be recognized clinically from other pelvic infections until it has progressed to the stage of pus formation. The diagnosis is never made clinically pre- or postoperatively until the chronic sinuses form, from which cultures can be made from the sulphur granules. By the time the diagnosis is made the process is so far advanced that hope of complete removal of the infection is remote. This probably accounts for the unfavorable results obtained in the cases reported to date. Serum agglutinations give confirmatory evidence but are not dependable.

Cornell collected 71 cases up to 1934. Of these 45 died, 8 were improved, 7 the outcome is doubtful, and only 11 are possible cures. He reports one case with a four-year cure. The infection involved both tubes and ovary. Bilateral salpingo-ovariectomy was done, patient was treated subsequently by potassium iodine. Of the 71 cases 50 involved the tube and ovary.

Schiller reported a fatal case in June, 1913, which was not included in Cornell's group. Since then Coté and Tudhope have reported 4 fatal cases of ovarian actinomycosis.

CASE REPORT

The patient, a forty-three-year-old colored woman born in Alabama, entered the Cook County Hospital on the Obstetrical Service, Mar. 9, 1936, complaining of pain in the right lower quadrant for ten weeks and amenorrhea for two months. Her last period began Dec. 30, 1935. On Jan. 1, 1936, a dull aching pain started in the right lower quadrant, and was continuous. She was treated conservatively

*Presented before the Chicago Gynecological Society, March 19, 1937.

and at the end of the month, Apr. 8, 1936, was taken to the operating room and an exploratory operation was performed. A large inflammatory mass was found which was thought to be too acute to remove and the abdomen was closed. The patient was instructed to return in six months for further surgery. She lost sixty pounds in weight during her stay at home.

The old wound appeared well healed and a large firm mass filling the pelvis and extending upward to the level of the umbilicus was found to the right of the midline. The lower abdomen was tender. The cervix was tender, movable, and took the Schiller stain well. Pelvic abscess was diagnosed, probably encapsulated in a tube or ovary because of the hardness and lack of fluctuation. Operation Oct. 22, 1936. Right-sided large tuboovarian abscess found with marked adhesions and pelvic peritonitis. Left adnexa normal.

Technique: Abscess was aspirated and most of the pus evacuated. Abscess sac was raised with difficulty from the culdesae and removed. Hemorrhage was slight and easily controlled. The wound had to be reopened about the fifth day and about three ounces of pus was removed. The wound then healed rapidly and the patient left the hospital Nov. 8, 1936. Cultures from the wound were negative for actinomyces. The report on the pathological specimen by Dr. Jaffe is as follows:

"The specimen consists of a mass 10 cm. in diameter; surface is deeply injected; on sectioning it contains a cavity 8 cm. diameter filled with a bloody material; wall is up to 20 mm. thick. Microscopic: The ovarian tissue is practically completely replaced by a granulation tissue surrounding multiple abscesses. A portion of an old corpus albicans is noted. Numerous giant cells are seen throughout the granulation tissue. Here and there typical clusters of ray fungi are noted. No tubal tissue is seen."

The patient was referred to the Research Hospital for deep x-ray therapy. She has regained 27 pounds in weight and feels fine. Small sinuses in the abdominal wound are still draining.

She has received four treatments of 325 r. units each between Feb. 16 and Feb. 24, 1937. These were applied anteriorly and posteriorly on the right side alternating. Each of these treatments is equal to a half of a skin erythema dose.

The patient had very little reaction to the x-ray, and is now getting potassium iodine ten drops three times a day, and increasing one drop each day. Further x-ray treatments are to be given, and because of the frequency of the infection to the opposite tube and ovary as noted in several cases in the literature, the left adnexal region will be x-rayed prophylactically.

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OVARIAN PREGNANCY*

A. E. KANTER, M.D., F.A.C.S., CHICAGO, ILL.

(From the Department of Gynecology of the Mount Sinai Hospital)

MRS. F. T., thirty-six years of age, was first seen on Jan. 6, 1937. She had been married for thirteen years and had been pregnant for the first time ten years ago when she aborted spontaneously at two months. Her last regular menstrual period occurred on May 25, 1936. On August 2, nine weeks after that period, she began to experience cramping pains in the lower abdomen. One week after this she began to bleed from the vagina, passing a small amount of blood constantly for a period of ten weeks after which there was a spontaneous cessation. Since that time the patient has remained in bed in order that the pregnancy might be retained. On November 28 the patient again began to pass blood from the vagina in small amounts, a condition that persisted until she was admitted to the hospital. During this entire period of time the patient had a poor appetite and as a result had lost thirty pounds.

General history was entirely irrelevant as was the general physical examination. Past history revealed that the patient had had attacks of tonsillitis, whooping cough, spastic colitis, and psoriasis. The menstrual history preceding the present difficulties was of no import, the periods having recurred at regular intervals and having been of average length. At the time of admission to the hospital the temperature was 97.8° F., pulse rate 72, respiratory rate 20, and blood pressure 108/76. The examination of the blood revealed a hemoglobin content of 75 per cent (Sahli), 3,390,000 red blood cells and 6,750 white blood cells with a differential count within normal limits. An Aschheim-Zondek test in November, 1936, was reported as positive.

On Jan. 4, 1937, the fetal heart sounds being absent, the patient was taken to the hospital in order that termination of the pregnancy might be accomplished. X-ray examination revealed a fetus that was projected over the upper cecal region and which was markedly smaller than was consistent with the period of amenorrhea.

At 10:00 P.M. of that day the patient was taken to the delivery room for the purpose of introducing a Voorhees' bag. It was found that the cervix could not be dilated sufficiently to allow for this procedure so a gauze pack was inserted into the cervix and vagina.

I first saw the patient on the morning of Jan. 6, 1937, at which time a bimanual examination revealed a cystic mass in the abdomen reaching just above the level of the umbilicus. The uterus was not enlarged over normal, was pushed over to the left by the abdominal mass, and the left vaginal fornix was thus obliterated. The uterus and cervix presented a firmness which is not ordinarily associated with pregnancy. A diagnosis of abdominal pregnancy was made and immediate laparotomy advised.

Abdominal section was performed on Jan. 6, 1937. Upon opening the abdomen it was found that the uterus was pushed over to the extreme left and was the size of a six weeks' pregnancy. There was a swelling the size of a large football, starting from the uterine horn on the right and extending behind the uterus, filling the entire pelvic area. Attached to the upper and lateral part of the mass was the sigmoid and small bowel. The mass was apparently an ovarian pregnancy with secondary rupture into the abdominal cavity. The sac was opened and a dead five

*Presented before the Chicago Gynecological Society, March 19, 1937.

months' fetus was removed, following which the mass was brought up and removed by means of clamps. A portion of the sac was left attached to the sigmoid. Peritonization was accomplished with the round ligament to the right horn of the

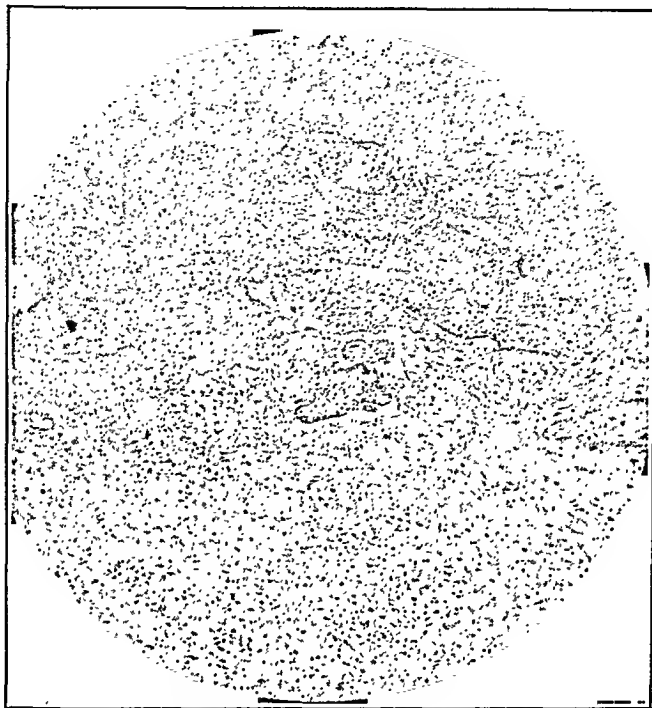


Fig. 1.—Chorionic villi in ovarian tissue.

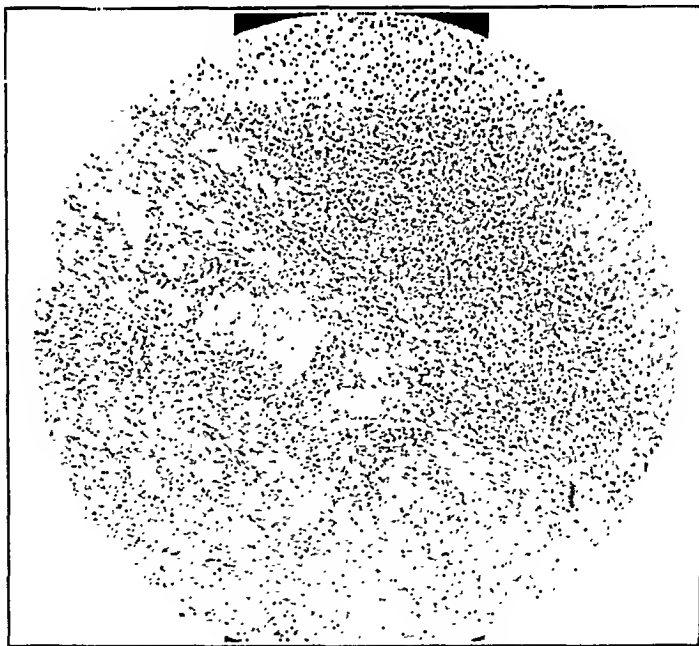


Fig. 2.—Decidual reaction and necrosis in ovary.

uterus. The right tube was normal and was not involved in the ovarian mass. The abdomen was closed without drainage.

After a slight rise in temperature during the first four days after operation the patient had an uneventful postoperative course and was discharged from the hospital on Jan. 15, 1937.



Fig. 23.

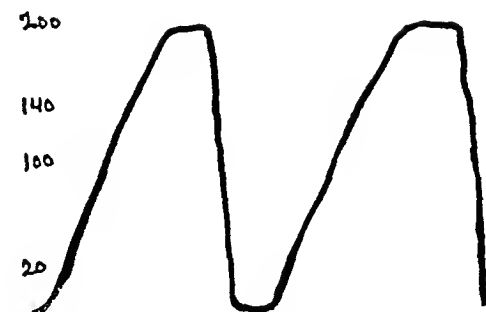


Fig. 24.

Fig. 23.—Case 6. First Rubin Test: The pressure rose twice to 200 mm. of mercury, and was maintained for half a minute. The patient had severe central abdominal pain at first, which gradually radiated to the right lower quadrant during the test, but no shoulder pains when sitting up.

Fig. 24.—Case 6. Second Rubin Test: After one month, the pressure rose to 200 mm. of mercury and was maintained the first time for three-quarters of a minute and the second time for one full minute. The patient complained of severe pain in the right lower quadrant during the test; but no shoulder pains when sitting up.

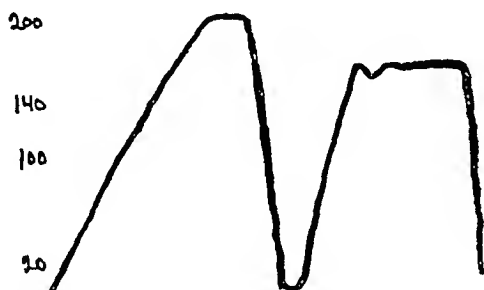


Fig. 25.

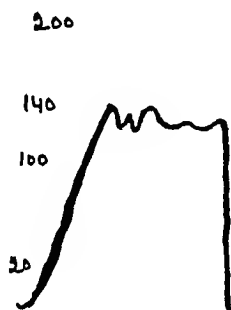


Fig. 26.

Fig. 25.—Case 6. Third Rubin Test: After ten diathermy treatments, the pressure rose to 200 mm. and was maintained for three-quarters of a minute and then allowed to drop. The second time the pressure rose only to 160 mm. and dropped to 150 mm. and fluctuated slightly around that point. The patient experienced slight right shoulder pain two hours after the test.

Fig. 26.—Case 6. Fourth Rubin Test: After eighteen diathermy treatments the pressure rose to a little above 140 mm. of mercury and then dropped to 130 mm. and fluctuated around 130 mm. with very faint tubal contractions. The patient complained of pain in the right lower quadrant during the test and pain in the right shoulder after the test.

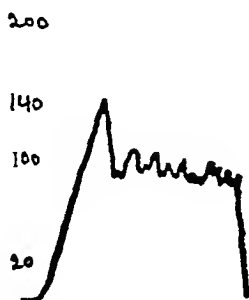


Fig. 27.—Case 6. Fifth Rubin Test: After twenty-two diathermy treatments the pressure rose to 142 mm. of mercury and then dropped to a little above 80 mm. and fluctuated between 80 and 100 mm. with fairly normal tubal contractions. This patient had severe shoulder pain three hours after the Rubin test. Four months after the last tubal insufflation the patient became pregnant and later gave birth to an eight-pound baby.

INTESTINAL OBSTRUCTION COMPLICATED BY PREGNANCY AT TERM*

RALPH A. REIS, M.D., CHICAGO, ILL.

FEW reports have been published of intestinal obstruction occurring in the second half of pregnancy or at term. There is a small number of reports of ileus occurring late in pregnancy but mechanical obstruction is most uncommon. Cornell,¹ Lazard,² Charbonnet,³ and Massey⁴ have reported mechanical obstruction in late pregnancy; in each of these instances, the obstruction was produced by an omental band or an adhesion, the freeing of which resulted in a return of intestinal integrity.

The following case is of interest because the intestinal obstruction had resulted in a gangrene which necessitated the excision of more than 200 cm. of ileum, immediately following a Porro cesarean section. There is apparently no similar case reported in the recent literature.

Mrs. E. W., a thirty-one-year-old primigravida, whose last menstrual period was on June 6, 1935, was first seen on March 1, 1936. She complained of generalized cramplike, abdominal pains which had been present for one month, and of excruciating abdominal pain associated with nausea and vomiting for the past twenty-four hours. This severe pain was rhythmic, cramplike, occurred every ten to fifteen minutes, and lasted thirty to sixty seconds. These severe pains, which were generalized at first, localized in the right lower quadrant after about eight hours. She had had two similar attacks before the onset of her pregnancy and one such attack, but without nausea or vomiting, about four weeks before the present one. At this time she had been given morphine for the pain which had been diagnosed as gall-bladder colic. Her previous history included a curettement and laparotomy for the removal of a uterine tumor and relief of uterine bleeding eight years previously.

Examination showed a patient writhing with abdominal pain, hiccoughing constantly, and complaining of recurrent nausea with occasional vomiting. Her color was good, the pulse was 80 and good quality, temperature 98.6° F. Abdominal examination revealed generalized tenderness most marked in the right lower quadrant, the point of greatest tenderness being about two inches above the umbilical level on the right side. Rebound tenderness was also marked on the right side, as was rigidity of the rectus muscle. The uterus was of a size corresponding to a thirty-eight weeks' pregnancy, was firmly contracted, with no periods of relaxation and was very sensitive to the touch. The fetus was lying in cephalic presentation and the fetal heart tones were strong and regular. Blood examinations showed no anemia and a leucocyte count of 13,400; examination of the urine showed no abnormalities. The patient was given a one-quart soap-water enema with no results.

The preoperative diagnosis was generalized peritonitis with intestinal obstruction due to appendicitis or postoperative adhesions. Gastric lavage was done, a dark fecal-like fluid being obtained. Ten per cent glucose solution was given intravenously, normal saline solution subcutaneously, and the patient was prepared for operation. The abdomen was opened by a paraumbilical right rectus incision, and about 50 c.c. of a turbid fluid was found in the peritoneal cavity. On drawing the gravid uterus forward into the incision, it was found that the entire posterior and right surfaces of the uterus were covered by densely adherent coils of small intestine, the majority of which were gangrenous. A cesarean section was then

*Presented before the Chicago Gynecological Society, March 19, 1937.

The pathologist's report as submitted by Dr. I. Davidsohn was: "Ovary: Specimen has the shape of a globular mass that has become deformed by a deep laceration. The outer surface shows some smooth areas, but in the most places there are evidences of loose recent adhesions. The color is pinkish red, purplish, and black. The consistency is quite soft. The whole specimen measures 14 by 11 by 8 cm. Enclosed within it is a cystic and partly opened cavity. One of its walls is made up by the bulk of the already described ovarian tissue. The other walls are considerably thinner and in the preserved portions measure from 1 to 8 mm. The inner surface of this cavity has an irregular and nodular appearance. Apparently a part of the cyst wall was left behind in the abdominal cavity. Attached to the inner surface is a thin membrane measuring about 11 by 5 cm. which has the appearance of a portion of fetal membranes. Section surface of the thickest portion of the wall is very hyperemic. It shows numerous hemorrhages. Separated from this specimen is an amorphous piece of tissue measuring 80 by 40 by 40 mm., having the identical structure as the main specimen. A nodule 20 by 12 mm. of a firm consistency and dark brown in color is present. It is 10 mm. long and has a thin pedicle. On section surface it shows, in the center, a brown amorphous tissue. A male fetus measuring 23 cm. having a macerated skin and being in a state of advanced decomposition is present. The cord measures 27 cm. and shows no gross abnormalities.

"*Microscopic:* Sections from the different portions of the specimen show decidual and placental tissue with extensive areas of necrosis and diffuse hemorrhages. At the periphery a narrow strip of connective tissue is present. In others ovarian tissue is present with some hyalinized areas and a great deal of blood pigment.

"*Diagnosis:* Ovarian pregnancy."

310 SOUTH MICHIGAN AVENUE

Di Gioia, A. M.: Studies of the Difficulties Encountered in the Friedman Test, and a New Modification Using Blood Serum, *J. Lab. & Clin. Med.* 22: 508, 1937.

The Friedman test has been reported as being practically infallible after the tenth day following the first missed period following suspected conception. But there have been many difficulties encountered in carrying out the test, the two important ones being shock following injections of urine and false negative or positive reactions. Shock following injection of urine may be due to too rapid injection, the taking of large doses of aspirin or quinine by the patient, inbreeding of rabbits, and extremely acid or alkaline urine. The reaction of the urine should have a pH which ranges from 6.8 to 7.4. False negative or positive reactions may be due to urine specimens obtained within a period less than ten days following the first missed period, in which case the pituitary hormone may not be excreted in sufficient quantity. The urine of patients having certain types of tumors (chorionic) may contain gonad-stimulating hormones.

To overcome these difficulties, Hoffmann's modification has been proposed. This consists in the withdrawal of 25 c.c. of patient's blood, centrifuging the specimen, and injecting 10 to 13 c.c. of the serum into the marginal ear vein of the rabbit. The rabbit may be autopsied within twenty-four hours. No figures are given, but it is hoped that this modification will supplant that in which urine has heretofore been used.

W. B. SERBIN.

ABERRANT SUPRARENAL GLAND TISSUE IN THE BROAD LIGAMENT*

JAMES A. GOUGH, M.D., CHICAGO, ILL.

(From the Department of Obstetrics and Gynecology, St. Luke's Hospital)

THE suprarenal gland, according to Goldzieher† develops from two primitive layers, the cortex from the mesoderm, the medulla from the sympathicus structure of the ectoderm. The medulla is formed from islands of cells originating from the sympathoblasts, later clumping together to form a definite layer in the mature organ. Isolated groups of medullary cells at times persist to form the so-called bodies of Wiesel and of Zuekerkandl.

The cortical cells spring from the "interrenal zone" of mesodermal epithelium lining the celome prior to segmentation. This zone extends from the glomus of the pronephros to the cloaca. Clumps of these cells proliferate, become pedunculated, separate from the celomic epithelium, and then coalesce to form the "interrenal organ," the precursor of the cortex of the suprarenal gland. Fusion of the medulla with the cortex occurs about the middle of the third month of intrauterine life. Many of the interrenal elements do not participate in the formation of the cortex but remain isolated, later undergoing regressive changes and finally disappearing. Persistence of such cell buds in postfetal life accounts for the so-called accessory suprarenal glands or Marchand's adrenals. In as much as only cortical cells are present, these names are misleading.

They occur most commonly in the vicinity of the adrenals, the kidneys, about the ovaries, testicles, broad ligaments, epididymis, and in the inguinal canals. The frequency with which they are found seems to vary with the type of observation. Anatomists state that they are very common, but clinical reports are decidedly infrequent. In *The Quarterly Cumulative Index Medicus* from 1932 to 1936, inclusive, the titles of only ten articles bearing on this subject are found.

M. A., a white woman, aged thirty-five years, and married fourteen, was admitted to the service of Dr. C. F. G. Brown at St. Luke's Hospital, Chicago, April 2, 1935. She complained of chronic indigestion characterized by anorexia, nausea, constipation, and abdominal discomfort of several years' duration; she said that she was nervous and slept poorly.

She had had two term pregnancies, one twelve, the other seven years before admission, both terminated by cesarean sections in another city. A thyroidectomy had been done in 1926. The family history was not significant. Menstruation had begun at the age of fifteen, had always been regular, of five days' duration, recurring every twenty-eight days, and occasionally painful.

General examination revealed a poorly nourished woman, extremely myopic, and weighing only ninety-three pounds. Her systolic blood pressure was 108/68. Examination of the chest, including a roentgen film, was negative. The abdominal wall was very thin, and an old lower left rectus scar was visible; no masses were palpable. Vaginal examination revealed no abnormal findings except the presence of a large amount of bowel in the culdesac. A blood count, including a differential,

*Read before the meeting of The Chicago Gynecological Society, March 19, 1937.

†The Adrenals, Their Physiology, Pathology and Diseases. Goldzieher, Max A.: New York, 1929, The Macmillan Company.

performed through a fundal incision, a normal healthy male child being delivered. The dense adhesions between bowel and uterus were dissected free. It was then found that the uterus, even though empty, was of a size which would prevent adequate exposure of the involved bowel and mesentery; a supracervical hysterectomy was therefore done.

Examination of the gangrenous bowel showed the involvement to be confined to the ileum. About 175 cm. were definitely gangrenous and the mesenteric vessels contained multiple emboli which involved apparently normal bowel on either end of the gangrenous portion. About 15 cm. of healthy bowel at each end was therefore included in the resection, 205 cm. of bowel being included. The intestinal continuity was re-established by a side-to-side anastomosis. The patient left the operating room in critical condition with a marked degree of shock.

The pathologic report was as follows: "The specimen consists of 205 cm. of small intestine. The serosal surface of one portion is dull, granular, and greenish red. Fifty centimeters from one end, firm adhesions bind neighboring loops of intestine. The lymphatics are markedly distended. The mucosa of the most distal portion is smooth and gray pink in color. Nine centimeters from the distal end, a sharp line separates this mucosa from a neighboring granular, raised, gray green red mucosa covered by necrotic membranous material. Fifty centimeters from the proximal end of the specimen, a line sharply separates darker gray black mucosa from the uninvolved portion. The greatest circumference of the bowel is 9 cm. The attached mesentery is hemorrhagic and thrombosed."

The postoperative course was most stormy, the temperature ranging from 101° to 104° F. for six days and pulse varying from 120 to 160, with a very low tension and of poor quality. During this time, a Wangenstein tube was in place constantly, continuous intravenous glucose was administered and the patient was given three transfusions of 500 c.c. each of whole blood on alternate days. The patient had a spontaneous bowel movement on the third day and thereafter had two to four small liquid bowel movements daily. On the sixth day, the Wangenstein tube was removed, fluids administered by mouth. The temperature reached 101° F. for twenty-six days after which it remained normal. A suppurating wound infection developed on the eighth day which drained spontaneously and continued to drain until the twenty-seventh day. The patient was discharged on the thirtieth day.

She has subsequently enjoyed good health, her only complaint being frequent small bowel movements with occasional, slight, momentary cramps. Tests of the intestinal motility show this to be more rapid than normal.

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104 SOUTH MICHIGAN AVENUE

Lucchetti, Giovanni: Triple Diagnostic Error in a Case of Pregnancy Complicated by Fibroid of the Uterus, Clin. obstet. 16: 520, 1936.

The author presents a case of pregnancy complicated by fibroid of the uterus in which were committed three diagnostic errors. The first error was made when the diagnosis of an ovarian cyst was made and disproved at operation. The second error was the failure to recognize the fibroid of the uterus. The third error was made when the fibroid was mistaken for a second fetus, revealed when the patient delivered only one fetus.

AUGUST F. DARO.

ERYTHROBLASTOSIS FETALIS AS A CAUSE OF INFANTILE MORTALITY*

A PRELIMINARY REPORT

CARL T. JAVERT, M.D., NEW YORK, N. Y.

(From the Department of Obstetrics and Gynecology, Cornell University Medical College and the New York Hospital)

THE present study is based on 10 cases which have been observed at the Woman's Clinic. Time does not permit a detailed report. Therefore, these remarks must be construed as a preliminary report. Studies are now in progress, and will form the basis of a subsequent communication.

The maternal records may be summarized as follows: The mothers averaged thirty-one years in age. Mediterranean ancestry was noted in 50 per cent of the cases. Multiparity was present in 9 cases. No familial incidence of the disease was observed. The Wassermann was negative in all. The hemoglobin averaged 83 per cent. Pregnancy was complicated by a poor weight gain in 50 per cent of the cases, and suggests a nutritional basis. An achlorhydria was found in one case so studied. The duration of pregnancy ranged from thirty-four to forty weeks with an average of thirty-seven weeks, indicating slight prematurity. Analgesia was used in 4 cases, and nitrous oxide anesthesia in 8 cases. Labor was short with an average duration of nine hours, of which the second stage was less than one hour. Delivery was spontaneous in 7 cases. Fetal distress was observed in 3 cases; 2 of which occurred in the second stage, while nitrous oxide was being administered. Both of these infants were delivered with forceps in order to obtain a living baby, but to no avail. The amniotic fluid had an amber color in 4 cases. A presumptive diagnosis of erythroblastosis was made before delivery in one case, and this case will be reported at a later date.

The placentas averaged 775 gm. in weight, which is about one-sixth heavier than normal. The fetal surface was distinctly yellow in 3 cases. On histologic section, erythroblasts were found in the fetal vessels.

The infants' records will now be reviewed. The sexes were about equal. The average weight was 3,457 gm. (7.5 pounds), which is excessive for infants of thirty-seven weeks' gestation. The edema and fluid in the serous cavities added to the increased weight. Resuscitation was necessary in 50 per cent of the infants. The rôle of analgesia and anesthesia in producing asphyxia can only be inferred. Edema was

*Read at the Section of Obstetrics and Gynecology, New York Academy of Medicine, January 26, 1937.

was entirely normal. Examination of several specimens of urine revealed a few red and white blood cells in the sediment. A kidney function test was normal, likewise an intravenous pyelogram.

The patient was anxious to be sterilized, and in view of her poor health, this seemed imperative. Accordingly, on April 17, 1935, under ethylene anesthesia, the abdomen was opened through a lower midline incision. Except for a marked ptosis of the stomach and intestines, no gross pathologic findings were noted. On the free edge of the right broad ligament midway between the uterus and the pelvic wall a tiny white object was seen. This was about a millimeter in diameter; at first it gave the impression of lying free in the peritoneal cavity, but was then found to be pedunculated. There was no surrounding inflammatory reaction. It resembled a healed tubercle or material encysted by the peritoneum. Slight capillary oozing followed its removal. Both tubes were ligated and cut and the abdomen closed



Fig. 1.—Cross-section showing suprarenal gland tissue. $\times 45$.

in the routine manner. The postoperative course was uneventful, the patient leaving the hospital eighteen days after the operation.

The following report is by Dr. Edwin F. Hirsch, Attending Pathologist at St. Luke's Hospital:

"In Zenker's solution is a tissue 3 by 2 by 1 mm. It is encapsulated, and has the structure of the cortex of the suprarenal gland. Fine fibrous strands extend from the capsule and separate cords of large cells with a foamy and granular cytoplasm. The cells are arranged as in the zona fasciculata. Best's carmine stain demonstrates the presence of a small amount of glycogen substance in the cytoplasm of the cells. The fibrous capsule is about 0.5 mm. thick, and outside of this is a little fatty areolar tissue. There are no inflammatory exudates."

A small mass of tissue discovered accidentally in the broad ligament proved to be a remnant of interrenal gland tissue with a structure corresponding to the cortex of the suprarenal gland.

intraeranian hemorrhage. The heart murmur presupposes a congenital lesion. The jaundice may lead to a conclusion of malformation of the biliary system. Aplastic anemia and leucemia must also be ruled out.

The incidence of erythroblastosis at the Woman's Clinic in 1936 was 1 in 400 infants. However, a study of the infantile mortality reveals even a greater incidence. Stander has advocated that all infants weighing over 1,500 gm., regardless of maceration or deformity, and those dying within the first fourteen days of life, be included in the total infant mortality rate. Of 110 infants so classified, 5 or 4.5 per cent were due to erythroblastosis. In the same year, 3 deaths were attributed to syphilis. Therefore, erythroblastosis exceeds syphilis as a cause of infantile mortality.

In conclusion, may I add that obstetricians are in a strategic position for the management of this condition, so that the present high mortality rate can be lowered appreciably.

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525 EAST SIXTY-EIGHTH STREET

DISCUSSION

DR. ARTHUR M. REICH.—The condition of erythroblastosis fetalis may recur in more than one offspring from a particular mother, as was demonstrated in a case of a colleague of mine. This patient had her first labor sixteen years ago, resulting in a normal living child. The second baby had hydrops and died in the first days. Then there were three babies in successive confinements, all showing similar findings and results, namely, icterus of the newborn and death on the third day of life.

Five years ago this same woman was attended in her sixth confinement by my aforementioned colleague who had not attended her before, but was acquainted with the previous history. He had an immediate diagnosis made by a blood examination on the newborn child. A transfusion was performed at once, followed by subsequent transfusions. The baby recovered.

DR. JAVERT (closing).—There have been no cases of familial occurrence in our series, although there are descriptions in the literature, particularly by de Lange, of several instances of hydrops and icterus gravis in successive infants born to the same mother.

noted in 3 cases, icterus in 5, pallor in 4, dyspnea in 6, and cyanosis in 5 cases. Convulsions were present in 3 cases, and a heart murmur in 2. Skin petechiae were frequently observed, and bleeding from the mouth and rectum was seen in 2 cases. The liver and spleen were usually enlarged.

The lowest red cell count was 1,300,000 per c. mm., with an average for the group of 3,400,000. The average hemoglobin was 51 per cent. The color index was 1.5. The nucleated elements ranged from 23,000 to 256,000 per c. mm.; of which 6 to 362 per cent were nucleated red cells.

The mortality was 70 per cent. The treatment was repeated transfusions. The 3 patients that survived received 9, 7, and 4 transfusions, respectively, in the first days of life. Within two weeks, the nucleated red cells had disappeared. These infants are now living and well. In England, Hampson uses human blood serum intramuscularly, with a mortality of only 6 per cent.

Autopsies were performed in 7 cases. The liver and spleen were invariably enlarged because of the hemopoietic hyperplasia. All patients showed an enlargement of the heart, and no cause for the cardiac murmur was found. Fluid was often present in the serous cavities, particularly in the pleural space, thereby contributing to the dyspnea and cyanosis. Petechiae were frequently observed on the mucosal and serosal surfaces. In the 3 patients that had convulsions, 2 had subarachnoidal hemorrhage, and the third had "kernicterus."

To recapitulate, erythroblastosis runs part of its course intra utero, and is recognizable at birth. The obstetrician is in a strategic position for diagnosis. His suspicions are aroused before delivery by the racial aspects, and a history of familial jaundice. A poor weight gain and an achlorhydria may also be premonitory. Hydramnios may be present. Diminished or absent fetal activity is suggestive. Fetal distress may occur. The amber-colored fluid when the membranes rupture is important. After making a presumptive diagnosis of erythroblastosis in the unborn child, all analgesia is interdicted, although rectal ether without quinine may be used for fetal distress. At the time of delivery, no nitrous oxide should be administered. Open drop ether may be used, although no anesthesia is preferred. The diagnosis is established after delivery by the deep yellow vernix, or the presence of hydrops. A palpable liver and spleen are confirmatory. The increased size of the placenta, with a yellow fetal surface or an edematous appearance, is additional evidence. Erythroblasts in the blood smear, and in the fetal capillaries of the placenta, complete the diagnosis.

Other conditions must be differentiated. Prematurity is associated with an increased number of nucleated red cells. Sepsis and congenital syphilis must be considered. The skin petechiae may lead to an erroneous diagnosis of hemorrhagic disease. The collapse and cyanosis suggest

On June 17, 1936, under nitrous oxide ether anesthesia an exploratory laparotomy was performed. At operation a bicornuate uterus was discovered, with marked thickening and inflammation of the left tube, the tube being about the size of a thumb. The right tube was normal in appearance. The left tube was removed. The appendix was slightly inflamed, and it also was removed. Smear made from pus in left tube reported as positive for gonococci.

The patient made an uneventful recovery until July 21, 1936, when it was discovered that the abscess in the posterior culdesae had re-formed. This was opened through the old incision and about 2 ounces of thick creamy pus was obtained. This wound continued to drain until Aug. 24, 1936, when the patient was last seen. At that time there was no discharge. Pelvic examination was negative and the patient felt fine.

AN AID IN THE STUDY OF STERILITY

ROY E. KRIGBAUM, M.D., F.A.C.S., COLUMBUS, OHIO

THOUGH most of the steps in the analysis of an individual case of sterility can be easily carried out in the physician's office, one offers especial difficulty, namely obtaining an adequate and undeteriorated specimen of the postcoital contents of the vagina. Ordinarily the physician resorts to one of three measures: He may call at the patient's home to secure the sample; he may provide in his office facilities for the intercourse of patient and husband and then proceed with his examination; or he may make an office examination of the patient after intercourse at home, with some loss of the contents by gravity during the trip.

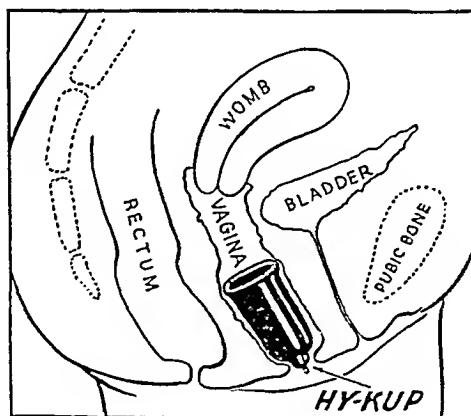


Fig. 1.

In an effort to escape the inconveniences of the first two measures and the impracticality of the third, the author has found what has proved in practice to be an ideal and simple solution—the employment of a bell-shaped rubber cup* originally devised for insertion into the vagina during the menstrual period. This device is $2\frac{1}{4}$ inches in length, $1\frac{1}{2}$ inches in outside diameter, and has a capacity of 30 c.c. It is soft and pliable and may be folded between thumb and forefinger for insertion. Upon its introduction into the vagina it resumes its original shape and adheres to the walls, forming an effective seal by suction. An elongated tip on the closed end

*Hy-Kup—The Hy-Kup Distributors, Indianapolis, Indiana.

UNILATERAL GONORRHEAL SALPINGITIS IN BICORNUATE UTERUS

H. C. JAMES, M.D., TUCSON, ARIZ.

UNILATERAL salpingitis in a bicornuate uterus is apparently a rather rare condition. The case which I am reporting at this time occurred in a girl thirteen years of age and was accompanied by a pelvic cellulitis with abscess formation in the posterior culdesac.

CASE HISTORY

Miss M. M., aged thirteen years, came to the office on May 26, 1936, with a chief complaint of vaginal discharge of about two months' duration. The onset was gradual and was not associated with pain. There was, however, a frequency of urination noted with the onset. The rest of the history of the present illness and the history by systems was of no consequence. Menstrual periods began when she was eleven years old. The periods were always regular, twenty-eight days apart, and lasting five to seven days. The flow was rather profuse but not associated with pain, backache, or headache. Last menstrual period May 16, 1936.

Past History.—Patient had pertussis at age of three years, otitis media at fifteen months, and the left ear has drained at irregular intervals ever since. She is deaf in the left ear. She had a tonsillectomy at twenty months and has had a scoliosis of dorsal spine since two years of age.

Physical Examination.—On inspection of the patient I was impressed with the precocious secondary sexual development, also the low tone quality of the voice. Her height was $57\frac{3}{4}$ inches, weight 94 pounds. Skin showed acne of face and neck. Her teeth were carious. Her thyroid was palpable, smooth and diffusely enlarged. There was a marked kyphosis and left scoliosis of spine with wasting of muscles of left shoulder. Her breasts were large, but there was no discoloration of nipples and no secretion present. Heart and lungs negative. Abdomen: short type with flare of ribs at the epigastrium; no pain nor tenderness. Pelvic examination showed introitus to be of the marital type, admitting 2 fingers with ease. There was a profuse foul vaginal discharge, greenish in color and rather thick in consistency. On entering the vagina there was a large fluctuating mass extending from under the symphysis to the posterior fornix on the left side. The mass was not particularly painful. It was impossible to outline the uterus and on speculum examination the cervix was very difficult to find; when found it revealed the point of exit of the discharge.

Laboratory Studies.—Blood, Kahn and Wassermann, negative; count normal; urine negative; smear: mixed bacteria—no gonococci.

On May 27, 1936, a posterior colpotomy was performed under nitrous oxide oxygen anesthesia and about 500 c.c. of foul smelling, thick, tenacious pus was obtained. Two Penrose drains were inserted. On June 3, 1936, all drains were removed. The pelvic discharge had stopped. Patient had no elevation in temperature and felt fine. Pelvic examination at this time revealed an irregular painless movable mass on the right side of the pelvis. It was decided at this time to follow with a course of Elliott treatments for a week to see what improvement or change would occur. At the end of one week there was no change and laparotomy was advised.

Success is less likely when the tubes are organically altered as in hydrosalpinx. There, a pressure of 200 mm. of mercury only rarely produces an artificial opening. Although a pressure greater than 200 mm. of mercury has opened strictured tubes, without the use of diathermy, I have not exceeded the maximum of 200 mm. of mercury advised by Dr. Rubin. I do not know how many of these cases may have been of this group, as I have not resorted to lipiodol injections of the tubes which Rubin has demonstrated produces inspissations and foreign body reactions which would render the already impaired tubal lumen hopelessly impermeable.

The observation of two cases of ectopic pregnancy in this group is of special interest. Though patency was reestablished in these two cases, the kymographie curve obtained in each during insufflation indicated very weak and shallow contractions at a relatively high pressure level. The curves obtained in the cases of normal pregnancy were rhythmic oscillations at a lower level, as in physiologic tubal patency. Rubin has called attention to the fact that ectopic pregnancy is more likely to develop in tubes the seat of adhesions and strictures where the pressure levels exceed 150 mm. of mercury as against normal intrauterine pregnancy where the pressure levels are about 100 mm. of mercury or less.

Tubal patency has been reestablished in a large number of cases by repeated tubal insufflation alone and to a lesser extent by diathermy treatments alone. It is very difficult to estimate just how much therapeutic value is to be accorded to the diathermy and how much to the tubal insufflation. In my opinion a greater number of successful cases will be obtained by the combined method of tubal insufflation and the diathermy, using the vaginoabdominal method.

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Gillies, C. D.: An Evolutionary Factor in Parturition: The Law of the Split Pelvis, Med. J. Australia 1: 778, 1936.

The split pelvis occurs in the predentate dinosaurs, birds and sporadically in certain orders of the mammalia. It has arisen in response to the demands of parturition also in the human female.

The underlying evolutionary principle is the law of the split pelvis, which states: When disproportion occurs between the products of conception and the pelvic brim, separation of the ventral symphysis occurs in those types which survive. In evaluating parturition allowance must be made for these evolutionary factors, which at present are independent of human control.

J. P. GREENHILL.

facilitates removal. It is free from any chemical compounds destructive to the sperm, such as are often found in condoms, and it may be boiled to insure perfect sterilization.

The procedure with the patient is as follows: She is carefully instructed in the method of inserting the cup and cautioned to sterilize it in boiling water prior to her use of it at home. It should then be wrapped in a clean handkerchief and laid near at hand for insertion immediately after intercourse. After she has adjusted the cup she is ready to come to the office for postcoital study. Two hours is suggested as the maximum interval between intercourse and the patient's arrival for examination. The patient is then put on the table and the cup removed by the physician. The postcoital contents are found to have been held in situ and intact, and abundant samplings can now be taken under optimum conditions to determine the number and motility of the sperm cells at various levels of the vagina and cervix, the presence or absence of pus cells, and the presence or absence of any cervical secretions destructive to the sperm.

This procedure has been used by the author over a period of four years and has been found uniformly satisfactory. It insures first of all a very adequate and fresh sampling of the postcoital contents and has as well the great advantage of saving the physician annoyance and time and the patient embarrassment and extra expense.

276 EAST STATE STREET

Robertson, Edwin: A Study of the Contractions of the Nonpregnant Human Uterus, *Edinburgh M. J.* 44: 20, 1937.

The results obtained with the intrauterine balloon method of recording contractions of the nonpregnant human uterus in the living subject show spontaneous activity of the uterus at various times from the beginning to the end of the menstrual cycle.

The results also show that in 11 out of 12 women, tested in the second half of the menstrual cycle, posterior pituitary extract caused increased muscular activity of the uterus.

WM. C. HENSKE.

Renton, Harold: Vaginal Discharge, *South African M. J.* 10: 808, 1936.

The author discusses the normal mechanism for the maintenance of vaginal acidity. The intricate power of the ovaries to effect changes in the glycogen content of the vagina and the ultimate production of lactic acid through the action of the Döderlein's bacillus are pointed out.

Pathologic discharges are primarily the result of infection. The organisms are usually of a mixed type—staphylococci, streptococci, coliform bacilli, and diphtheroids are the most common. Gonococcal and parasitic infections are separate entities. The trichomonas is the most common parasite producing discharge.

Frequently a vaginal noninfective leucorrhoea is present. A hormonal disturbance may be the basis for this.

Trichomonas vaginalis is described, as well as methods for examining and staining the parasite. Treatment for leucorrhoea is outlined.

F. L. ADAIR AND S. A. PEARL.

Society Transactions

OBSTETRICAL SOCIETY OF PHILADELPHIA

MEETING OF MARCH 4, 1937

The following papers were presented:

A Case Report of Solitary Endometrial Cyst of the Sacrouterine Ligament. Dr. S. Leon Israel.

Report of a Visit to Middlesex Hospital, London, Eng., and to the Radiumhemmet in Stockholm, Sweden. Dr. Brooke M. Anspach.

The Use of Diathermy in Gynecologic Out-Patient Clinic. Dr. Edward F. McLaughlin.

Experience in the Treatment of Carcinoma of the Fundus of the Uterus With Five Year End-Results in Forty-Seven Patients. Dr. Lewis C. Scheffey and Dr. William J. Thudium. (For original article, see page 1006.)

CHICAGO GYNECOLOGICAL SOCIETY

MEETING OF MARCH 19, 1937

The following papers and discussions were presented:

Intestinal Obstruction Complicated by Pregnancy at Term. Dr. Ralph A. Reis. (For original article, see page 1038.)

Ovarian Pregnancy. Dr. A. E. Kanter. (For original article, see page 1035.)

Biology of the Human Vagina in Pregnancy. Dr. M. Edward Davis and S. A. Pearl. (To be published.)

Actinomycosis of the Ovary. Dr. Frederick H. Falls. (For original article, see page 1033.)

Aberrant Suprarenal Gland Tissue in the Broad Ligament. Dr. James A. Gough. (For original article, see page 1040.)

Pseudohermaphroditism. Dr. H. O. Jones.

Multiple Carcinoma Occurring in Two Patients. Dr. Fred O. Priest.

Bone Changes in the Fetus Following the Administration of Dicalcium-Phosphate and Viosterol to the Pregnant Woman. Dr. G. C. Finola, et al. (For original article, see page 955.)

BROOKLYN GYNECOLOGICAL SOCIETY

MEETING OF MARCH 5, 1937

The following paper was presented:

The Stillbirth Problem. Dr. Philip F. Williams, of Philadelphia (By invitation). (For original article, see page 940.)

MEETING OF APRIL 2, 1937

The following papers were presented:

Abdominal Pregnancy Near Term, Operation and Hormonal Studies of the Blood and Urine With the Placenta Left in Situ. Dr. A. S. MacGregor. (For original article, see page 1030.)

The Theca, Granulosa, Lutein Cell Tumors of the Human Ovary and Similar Tumors of the Mouse's Ovary. Drs. H. F. Traut and J. S. Butterworth. (For original article, see page 987.)

Editorial

Factors Responsible for Failure Further to Reduce Infant Mortality

THE first report of a survey by the Board of Health of Chicago of the deaths of infants less than thirty days of age was published during the summer of 1936.* From this report Bundesen and his co-authors concluded that efforts to reduce neonatal mortality must be centered upon the control of the causes of death at the time of birth of premature babies. A new report† somewhat modifies this conclusion and lessens the stress laid upon simple prematurity. Attention is now drawn to the difficulty of attacking the problem of neonatal death, when the relative frequency of the different causes of death in this period is so little known. Ordinary statistics frequently misrepresent the true importance of various special causes. These errors result partly from the rather rigid classification imposed by the *International List* and the *Manual of Joint Causes*, and partly from the fact that the statistics are usually based on groups of cases, a large proportion of which have not been subjected to competent postmortem examination.

The rules of the official classification result particularly in many deaths being classified as due to prematurity when they are actually the result of other causes. Thus, when 1,123 neonatal deaths were officially classified, 44.6 per cent were assigned to premature birth; while among 398 deaths studied by satisfactory necropsies, there were only 82, or 20.6 per cent, in which the only known factor responsible for death was the prematurity. With this reduction, as the result of postmortem examination, in the importance of simple prematurity as a cause of death, there occurred a definite increase in the frequency of intracranial hemorrhage, a slight increase in congenital malformations, and a tripling of the relatively infrequent deaths from pneumonia.

The comment is rightly made that before procedures can be effectively carried out to reduce the number of deaths in the neonatal period, the causes of these deaths must be accurately determined. This can be done only by large series of competently performed autopsies and by a system of classification which will bring out the essential point in the loss of each infant.

*Bundesen, H. N.; Dahms, O. A.; Frohbein, W. I.; and Harmon, G. E.: Mortality of New-Born Infants in Chicago during 1935, with Special Reference to the Premature, J. A. M. A. 107: 270, 1936.

†Bundesen, H. N.; Frohbein, W. I.; Dahms, O. H.; and Potter, E. L.: Factors Responsible for Failure Further to Reduce Infant Mortality, J. A. M. A. 109: 337, 1937.

After reading these excellent reports, one is struck by the pertinence of the conclusions in two respects. For the individual obstetrician nothing is more valuable than to see the ill effects of his own unsuccessful operation. The demonstration of intracranial hemorrhage and tears of the tentorium or falx after a forceps delivery or a broken neck after a breech extraction cannot fail to impress the operator with his responsibility. Such mental acceptance of responsibility is far too easily avoided when the death can, without necropsy, be assigned to such "natural causes" as asphyxia or atelectasis. From a constructive viewpoint visualization of the mechanical effects of traumatic procedures will go far toward teaching the operator what modifications he must make in the mechanics of his own technique of delivery.

The wider point brought out is that without accurate statistics the campaign against neonatal deaths is without definite objectives. To obtain such statistics there must be more necropsies and a revision or rejection of the official rules for classification of the causes of death in this group of cases. This calls first for coordinated efforts on the part of hospitals to supply data from sufficiently large groups of necropsied cases and, second, for action by some suitable body concerned to agree on a better system of assigning causes of death in the neonatal period. The latter may be the proper work of a Board of Health or of one of the national medical societies.

In spite of technical difficulties in the collection of accurate statistics, the investigators permit themselves certain definite conclusions that their investigations to this point have led them. This study has shown that four main causes which contribute greatly to infant death are: (1) maternal complications, such as a toxemia and placenta previa, for such maternal complications were present in 385 out of 1,123 neonatal deaths; (2) inexperienced obstetric care, for cerebral hemorrhage was the most frequent cause of death (25.6 per cent) in the infants upon whom necropsies were performed; (3) prematurity; (4) incorrect or inadequate neonatal care. With these causes the obstetrician will in general agree, although he will certainly plead that the full quota of cerebral hemorrhages be not assigned to "inexpert obstetric care."

Emphasis may shift with the changes in the system of assigning causes of death, but with these studies the general direction of attacking the problem of neonatal deaths is indicated. The work of the Chicago investigation is most important. It deserves to be copied and to receive whatever cooperative support is needed.

Department of Reviews and Abstracts

CONDUCTED BY HUGO EHRENFEST, M.D.

Collective Review

MENSTRUATION AND ITS DISORDERS

A CRITICAL REVIEW OF THE LITERATURE FROM 1933 TO 1936 INCLUSIVE

HUGO EHRENFEST, M.D., ST. LOUIS, MO.

(Concluded from page 729, October Issue.)

XII. MENARCHE

Newer investigations in regard to age of menarche and the various factors which determine the appearance of the first menstrual flow vary in their results. Engle and Shelesnyak²⁵⁷ found that of 250 Jewish girls in a New York Orphan Asylum by far the larger percentage had their first flow in the winter months, while amenorrheas will occur more often in the summer months. According to Ishizaka²⁵⁸ also among Japanese girls, the menarche most often appears in the cold winter months, as a rule at an earlier age in those living in cities. The same facts were ascertained by Yosioka²⁵⁹ who studied 1,172 Japanese college students. December showed the highest incidence of first menstrual flows. Most extensive statistical researches, covering all parts of Japan, made by Tomii,²⁶⁰ in contrast tend to prove that first menstrual flows most often appear in the spring, the least often in winter.

Chinese statistics, presented by Yang and Gear,²⁶¹ are based on the study of 2,924 girls. In about 58 per cent of them, menarche occurred in spring or summer, and at a considerably earlier age than among European people. Investigating Polish women in Wilno, Luezyński²⁶² found that in Jewish girls the menarche occurred about one year earlier than in non-Jewish women, in his opinion, expressing the great importance of the factor of race, and the unimportance of environment. Skerlj²⁶³ claims that Norwegian statistics support the idea that menarche is influenced by climate, a view practically identical with that given by Areseheff²⁶⁴ after a study of menarche in Armenian girls.

Kennedy's²⁶⁵ conclusions are drawn chiefly from notations found on the hospital records of 10,000 female patients. The age of menarche for Edinburgh is not significantly different from that reported from Italy or Russia. Figures from Prussia, however, give a decidedly higher average age, and those from Rio de Janeiro, on the other hand, are much lower. In his opinion, it can be deduced that climatic differences probably are inoperative but that environmental agencies apparently play a rôle. No correlation was found by him between early or late menarche and high or low fertility.

In the opinion of Peller,²⁶⁶ a recognized authority in biometric statistical studies, climatic influence certainly is smaller than commonly considered to be. The psychic factor is of considerable importance and excitement over a birthday celebration in all probability accounts for the rather frequent appearance of the first menstrual flow on a birthday or at least within the month of the birthday. Obviously such a psychic factor can become operative only if the development of the genital sphere is sufficiently advanced to permit such a reaction to an emotional stimulus. The physical development in its last analysis, however, is greatly affected by such external conditions, as environment, food supply, place of living, work, and state of health.

Among the diseases of childhood which retard menarche, Dworzak²⁶⁷ assigns first place to rachitis. For this reason women with a late menarche show so high an incidence of pelvic anomalies. Also Tranquilli-Leali²⁶⁸ claims that, in most women, whose menarche occurred too early or rather late, the pelvis will be found to be abnormal. Weysser²⁶⁹ refers to Feldweg's earlier report that women with earlier or unusually late menarche in large numbers develop menstrual disorders or have pathologic deliveries. Weysser can only confirm this observation as far as pathologic labors are concerned. He made also the following differentiation: Difficulties of labor in women with delayed menarche were found to be due to pelvic anomalies, while in those with early menarche, the difficulties were due rather to abnormal resistance of the soft portions of the birth channel. A control study, very recently reported by Risopoulos,²⁷⁰ fully confirms Weysser's finding in regard to the relation of late menarche to obstetric complications, but fails to support his claim regarding an effect of early menarche on the soft tissues of the lower birth canal. Weysser in his conclusions stresses the significance of constitution in the age of menarche.

The rôle played by constitutional variations in the occurrence of menarche and menopause is most interestingly discussed by Julius Bauer.²⁷¹ In the germ plasma of the fertilized ovum are determined the chief characteristics of the life of an individual and with them the rate of his evolution and involution. But obviously, environmental factors in this respect will exert some influence at some time or another. The causes for the menarche thus are genotypically fixed, but alterations are possible through the harmful effect of intervening disease on the various endocrine elements which conjointly lead to sex maturity. Involution of ovarian activity can be entirely independent from the general phenomena of senescence.

Very similar ideas are expressed in Ploss-Bartels *Woman*.¹⁹⁵ The earliest available material led us to suppose that climate and especially temperature were the main factors in retarding or hastening the first menstrual period, but all newer material leaves no doubt that these influences are rather unimportant in comparison with those of the internal secretions, food, habits and manner of life, and racial stock. Social class and habitat are closely related to early or late sexual stimulation and experience, but the internal glands determine constitutional variations of different "endocrine blends" (Mathes). They are expressed in such opposite types as "pyknie" or "asthenico-ptotic," the latter being the more common in women with menstrual disorders.

Most convincingly Breipohl²⁷² shows that all scientifically valuable investigations on menarche must be based on data more reliably pro-

cured than heretofore. Information obtained from patients or their parents rests solely on usually inaccurate memory. In his opinion, the best method in this respect is the one officially introduced in Koenigsberg. Every school teacher is required to make a record of the exact date when one of her little pupils has her first menstrual flow.

As a valuable statistical study we may quote one made by Petri.²⁷³ He collected data from large families with several female children. Thus he could make comparisons between the ages of menarche of the mother and all her daughters. Comparative investigations were also made between various groups of girls, even on 100 pairs of female twins. In all the different groups, outside of twins, the average age of menarche varied within so wide limits that the strikingly small variations in the 51 pairs of uniovular and 47 pairs of biovular twins must be accepted as pointing clearly to a definite causal relationship between hereditary factors and time of sexual maturation.

An instance of unusually early menarche is reported by Stiasny.²⁷⁴ Menstrual flows began at the age of one year. When two and one-half years old, the child had well-developed breasts, pubic hair on the mons veneris, and fully developed external genitalia. At that time, she flowed regularly every four weeks. Mayer's¹³³ statement that precocious menarche often impairs later development and reduces survival chances is in accord with the known fact that premature ovarian activity rather frequently is directly due to some complicating pathologic condition.

Kraus²⁷⁵ deals with the frequently reported association of hydrocephalus with sexual precocity. He investigated the relation of increased intracranial pressure to disturbances of the pituitary gland. It seems that in patients with neoplasms of the brain or meninges, or in patients with chronic internal hydrocephalus the anterior lobe of the pituitary becomes either underactive or overactive, depending on the particular changes in the hypothalamic region.

In a discussion of granulosa cell tumors of the ovary, characterized by production of large amounts of estrogenic substances, Novak and Gray²⁷⁶ refer to the fact that precocious menstruation may be due to various endocrine anomalies. Its occurrence in association with a palpable ovarian tumor should always lead to the suspicion of a granulosa cell tumor. Bland and Goldstein²⁷⁷ made hormoneologic studies on a child, six years old, with precocious sexual development. The latter finally was definitely traced as due to bilateral granulosa tumors. They found 8 similar reports to date in the literature.

The first bio-assay of estrogen hormone contents of a granulosa cell tumor has been reported by Gospe.²⁷⁸ He found 3.2 M.U. per gram of fresh tumor tissue and 36 M.U. per gram of desiccated tissue. Naturally these findings do not express the actual capability of this tumor to produce estrogenic substances. Occasionally they exert a luteinizing effect and cause amenorrhea as shown by Benda and Kraus.^{278a}

XIII. DELAYED MENARCHE—PRIMARY AND SECONDARY AMENORRHEA

It is more convenient to discuss delayed menarche, primary and secondary amenorrhea together, because these three anomalies of menstruation have many causative factors in common and call for rather similar therapy.

It is common practice to speak of *delayed menarche* if the first menstrual flow has not appeared at an age of about sixteen, and to diagnose

primary amenorrhea if the still amenorrheic woman is older than eighteen. No agreement exists in regard to a clinical differentiation of a long interval menstruation from a *secondary amenorrhea*.

Newer literature on either delayed menarche or primary amenorrhea deals chiefly with such causes as underdevelopment of the uterus, non-initiation of ovulation, and failure of the endometrium to pass through the typical changes of the cycle. They all are dependent more or less directly on abnormal (not necessarily deficient) activity of various endocrine glands and not solely of the ovaries.

With the present acute interest in the physiology and pathology of the endocrine system and the great faith in the therapeutic efficacy of hormone extracts, medical literature of the past few years abounds in reports concerning scientific investigations of the complex interrelations between the entire endocrine system and menstrual function (estrus in various animals), and contains many, more or less reliable, clinical contributions describing results (chiefly good) obtained with certain organ extracts in the treatment of the various disorders of menstruation.

These introductory remarks seemed necessary to explain why the following pages present a survey of only a relatively small part of this literature. We attempted to select only those papers, experimental and clinical, which can be considered of theoretical and practical interest and value to the practicing gynecologist. Since many of them discuss etiology and therapy of all types of disordered menstrual function, it was at times impossible to limit quotations to those dealing specifically with amenorrhea.

Disordered menstrual function, as a matter of fact, is but a symptom complex and, therefore, its appropriate treatment necessarily is determined by the exact diagnosis of the underlying cause which in itself (e.g. deficient ovarian endocrine function) may represent only the effect of still another cause (e.g. abnormal activity of another endocrine gland). As emphasized, among others, by Benthin²⁷⁹ the task of discovering the basic etiology in the individual case is a very difficult one. The attempt to fit all these varying primary and secondary causes into a comprehensive and presumably useful schematic arrangement inevitably becomes a very complex problem as can be gleaned from the tabulation offered, e.g. by Crossen and Crossen.²⁸⁰ Many writers are willing to agree (e.g. Josef Novak²⁸¹) that in a large number of amenorrheas the true cause cannot be discovered. Even the most elaborate classifications obviously cannot solve the problem of correct diagnosis, because, e.g. in amenorrhea, such vague factors as change of domicile (girls entering college or training schools for nurses), chilling, emotional shock, etc., admittedly play an important rôle. Masearetti²⁸² describes a hysterical woman who periodically becomes amenorrheic whenever she thinks that she is pregnant. Literature contains many reports of such imaginary pregnancies even associated with secretion of true milk in nulliparous women (as I observed in one of my patients). As previously mentioned, Theobald⁶⁶ ascribes anomalies in the rhythmicity of the menstrual function to functional disorder of a special center in the hypothalamus controlling periodicity. Kreis,¹⁰ who believes in an independent rhythmicity of endometrial changes, logically concludes that oligomenorrhea or amenorrhea cannot be accepted as proof of an existing ovarian deficiency, that even under these conditions the ovulation process may proceed normally. Also Robert T. Frank⁴⁹ states that

amenorrhea, oligomenorrhea, and functional bleeding of any sort are unreliable as positive indices of ovarian function.

Almost two decades ago German medical literature extensively discussed the many unaccountable aspects of the so-called "War amenorrhea." This particular form has disappeared since then, and its place in Germany, at the moment, is taken by another inexplainable amenorrhea, succinctly termed by Nordmeyer and Howe²⁸³ the *Landjahr Amenorrhea*. It occurs in young girls between fourteen and fifteen years old who, on account of impaired health or solely "for the purpose of protecting them against politically dangerous surroundings," after graduation from public schools, are systematically removed, for approximately eight months, from the larger cities to rural districts to become familiarized with agricultural life and work. Investigations have revealed that, within one large group, out of the 89.6 per cent of girls menstruating regularly at the beginning of this service, only 27.3 per cent were still regular at its termination. Of the 10.4 per cent menstruating irregularly at the start, all with the exception of one had become amenorrheic, which together with temporary or complete cessation of flows during the time of service brings the total of amenorrheic girls in the entire group at the end of the *Landjahr* to 64.9 per cent, with about three-fourths of them not having menstruated since admission to the service.

Comparisons with groups of girls assigned to other types of work lead the writers to the conclusion that the only cause for this amenorrhea could be the fact that they were living in a special part of the country under a particular climate. They feel that there is every reason to assume that this unfavorable effect is only temporary and will not affect later menstrual or reproductive function of these girls. However, it seems pertinent to mention in this connection a recent paper of Wehefritz and Gierhake,²⁸⁴ in which they discuss the present, striking prevalence in Germany of uterine hypoplasias. They arrive at the conclusion that a steadily increasing incidence of uterine hypoplasia, usually ascribed to ovarian deficiency, can be satisfactorily explained only on the basis of deficient diet in the post-war period when these women were approaching puberty. In the light of recent information, it seems likely that an insufficient amount of vitamins in this respect played the most important part.

It is generally appreciated that secondary amenorrhea frequently appears as an early sign of tuberculosis. Therefore, the careful physical examination required in every case of interruption of heretofore regular menstrual function must include a study of the lungs. Gal,²⁸⁵ contrary to prevailing views, believes that the amenorrhea in these patients is caused not by the disease or a tuberculous toxin, but more likely is due to a pathologic constitution which predisposes the woman to a tuberculosis infection. In some tuberculous women, the amenorrhea may be the result of destruction of endometrium or ovaries, involved in the process. Gal concludes that in the majority of these patients it will hardly be necessary to attempt restoration of the menstrual function by endocrine or any therapy. Kriech¹⁶⁹ goes even farther. He states that the use of ovarian preparations to counteract menstrual disorders in tuberculous women frequently aggravates the tuberculous process.

The complexity of relationship between amenorrhea and ovarian function is clearly evidenced by a report of Stein and Leventhal²⁸⁶ in which they describe cure of amenorrhea in seven cases by means of resection of bilateral, small cystic degenerated ovaries. As is well known, small cystic degenerated ovaries, almost characteristically, cause profuse bleeding from a hyperplastic endometrium, developed under overstimulation by an excess of estrogenic substances originating in the many small cysts, all lined by granulosa cells. Stein and Leventhal account for amenorrhea in association with polycystic ovaries and for the good results secured with resection in the following manner: Small cystic degeneration of ovaries is induced by an excess of anterior pituitary hormones. The amenorrhea is due to mechanical conditions within the ovaries. Crowding of the ovarian cortex by the cysts interferes with maturation of the small follicles which are pressed down deep into the ovarian substance.

Much interest has lately developed concerning the endocrine activities of certain ovarian newgrowths. We have previously spoken of the estrogen producing granulosa cell tumors which may lead to precocious menarche. Another type of ovarian tumor, in accord with Robert Meyer's suggestion generally termed arrhenoblastoma, is characterized by masculinization (i.e. defeminization) of the patient. The earliest symptoms comprise lengthening of the menstrual intervals until amenorrhea is established, accompanied by atrophy of uterus and breasts. Then follow changes in all the secondary sex characteristics to those of the male. In women, below the climacteric age, removal of the newgrowth causes gradual subsidence of virilism with restoration of normal menstrual function. Even instances of subsequent pregnancies have been reported. Recurrence of the neoplasm again causes masculinization of the patient. An exhaustive survey of the literature on arrhenoblastoma recently has been published by Fauvet.²⁸⁷

Also the adrenal cortex produces a hormone which is of importance in the development of the secondary sex characteristics. With certain tumors of the adrenal glands hirsutism and amenorrhea develop regularly. Thus, as pointed out by Saphir and Parker,²⁸⁷ the symptoms of an excess of adrenal cortex hormones are practically identical with those of an arrhenoblastoma. These writers report a case of typical adrenal virilism in which the adrenals were found to be seemingly normal, but aberrant adrenal cortex tissue was discovered in an ovary. They state that increased adrenal cortex function seems to be associated with increased excretion of estrogenic substance in the urine, a fact seemingly contradicting prevailing conceptions but theoretically explainable.

Ever since the classic researches of Leo Loeb, it has been known that a persistent corpus luteum (or corpus luteum cyst) inhibits ovulation and causes amenorrhea. Therefore, we wish to mention in this connection the statement of Hamblen and Ross²⁸⁸ that administration of the anterior pituitary-like luteinizing factor may cause degenerative processes in the ovaries, seemingly often resulting in formation of follicle cysts and persistence of the corpus luteum. They add that these changes possibly are only temporary and thus do not represent a permanent damage.

Normal menstrual function depends on normal anterior pituitary function. Clauberg and Breipohl²⁸⁹ confirm the claim of various preceding investigators that normal gonad function is determined by an

A STUDY OF ONE HUNDRED CONSECUTIVE CASES OF ECTOPIC PREGNANCY

R. M. GRIER, B.S., M.D., F.A.C.S., EVANSTON, ILL.

*(From the Department of Gynecology and Obstetrics of Northwestern University
Medical School and of the Evanston Hospital)*

IN DECEMBER of 1930 the author reported in this JOURNAL a study of fifty consecutive ectopic pregnancies cared for at the Evanston Hospital in the Department of Gynecology and Obstetrics. They occurred during the period from Jan. 1, 1922, through the first half of 1928 (to July 1, 1928). There have been fifty more since then to Jan. 1, 1936, fourteen years in all. This was an average incidence of seven cases per year. In the latter number there have been two deaths, whereas in the former there was only one. This makes a mortality of 3 per cent for the one hundred cases.

As in the first report, an attempt has been made to correlate ideas which would be helpful in diagnosis. In the study of these histories, we found that in many cases the onset was insidious, there being nothing at first which alarmed the woman or attracted the serious attention of the physician. Amenorrhea is the first symptom that should arouse the patient's suspicion. This was present in 76 per cent. Thus 24 per cent apparently did not "miss a period." The accuracy of this latter statement is open to question. Irregular bleeding was a most common symptom, being reported in 88 per cent. The initial bleeding was often considered by the patient as her last regular menstrual period. But on careful questioning, a period of amenorrhea, that is a cycle of more than twenty-eight days, was discovered. Too often these women did not consider this bleeding of much consequence, and allowed it to continue until other symptoms developed. Usually associated with the amenorrhea and bleeding there were subjective symptoms of early pregnancy, such as breast changes, nausea, and drowsiness. The pelvic discomfort was greater than that usually present in a normal intrauterine pregnancy. There were cramplike pains on one side or the other which varied in severity. In this series three women who had had previous ectopic pregnancies reported to their physicians with no more than the above-mentioned symptoms. In all three cases a tubal pregnancy was found. Most women considered themselves pregnant and threatening to abort or to have aborted. Many women stated that they had passed a pink piece of tissue which they considered products of conception. Seven times this was saved and brought to the hospital for microscopic examination; the pathologist reported a "decidual cast of endometrium"

luteinization in the follicles. Equally ineffective proved injections of antuitrin-S given to an immature animal over a period of two months to a total of 16,500 R. U. Roek and Bartlett²⁹⁶ gave anterior pituitary-like extracts in moderate doses, intramuscularly, to a total of between 1,500 and 3,500 R. U. to amenorrheic women. Such doses failed to stimulate the ovaries sufficiently to cause any structural alterations of the endometrium.

We had already occasion to mention that Campbell¹⁶⁵ had no results with emmenin in the treatment of primary amenorrhea. Goldberg and Lissner²³⁶ tried this preparation in 100 instances of menstrual disorders. It proved helpful in secondary amenorrheas of less than one year duration. They state that in practice the use of this substance of necessity will be extremely limited on account of its high price, which reminds one of a concluding remark made by Davidson²⁹⁷ in a paper dealing with the use of estrin and progestin in the treatment of secondary amenorrhea: "Considering that a course of treatment, following the technique here described, costs about four guineas, and that to guarantee a result at least two courses are necessary, most probably three, it is obvious that this treatment can be administered only to a chosen few. Even then it is probable that only two or three periods will result in the majority of cases."

This offers an opportunity to emphasize that in the larger number of clinical reports the appearance of the first and probably only flow following organotherapy is considered sufficient to classify the result as satisfactory and, not so rarely, to count the case as "cured." However, Dunn²⁹⁸ reporting results of hormone induction of menstruation in 5 cases of amenorrhea of from three months to nine years duration (including one girl thirteen years old!) lays particular stress on the fact that by giving progynon B in daily doses of 90,000 R. U. to a total of 1,126,000 R. U. he was able to secure three consecutive flows after an amenorrhea of nine years in a woman forty-three years old.

Winter²⁹⁸ finds from his experience that a secondary amenorrhea in a woman, who up to that time has menstruated regularly, rather calls for a thorough physical examination and most probably will not be cured by organotherapy. Practically the identical statement is made by Kaufmann.²³² He adds that if in such amenorrheic patients an endometrium capable of reaction is present, and if after administration of sufficiently large doses of follicular followed by corpus luteum hormones, a flow actually appears, only in about 25 per cent of the cases the cycles will continue spontaneously. Frank²¹ reminds us that the majority of amenorrheas and menorrhagias are of a transient nature.

We have mentioned low-dosage irradiation of the pituitary gland and ovaries as a substitute for administration of anterior pituitary-like substances. A very detailed description of this form of x-ray therapy has been furnished by Wittenbourg and Porkhovnik.²⁹⁹ Mazer and Spitz²³⁹ qualify as a "stimulating dose" one only slightly larger than that employed in diagnostic procedures. Such a dose leads to an increase in cell activity without causing any histologic alterations discoverable in microscopic study. The stimulation of cell activity is due solely to biochemical factors. They warn that often repeated "stimulation" may cause "irritation" which may finally end in destruction of cells. "Restoration of ovarian function and of menstrual periodicity through low-dosage irradiation is evidence of true stimulation." The ovaries

equilibrium between the hormones of the anterior pituitary and of the gonads. They showed by experiments that the anterior pituitary gland of castrated animals exhibits characteristic structural changes and contains a larger amount of gonadotropic hormones. Structure and hormone output become again normal under the administration of either follicular or corpus luteum hormones. In this connection must be mentioned a paper of Frank and Salmon²⁰⁰ in which they demonstrate that the administration of follicular hormone (progynon B) leads to the disappearance of the gonadotropic factors of the anterior hypophyseal gland from blood and urine of women past the menopause. Excessive or prolonged estrin therapy, according to Emil Novak²³⁰ actually inhibits the normal activity of the anterior pituitary which is so essential for the menstrual mechanism. "Since estrin does not influence ovulation, it obviously has no place in the treatment of sterility associated with amenorrhea." Sevringhaus²⁹¹ warns against the treatment of primary amenorrhea with ovarian preparations because larger doses will further inhibit the presumably already deficient activity of the anterior pituitary gland. However, literature is not wanting in reports of good results with ovarian extracts in amenorrhea.

Kaufmann²⁹² specifically stated that in cases of primary amenorrhea with underdeveloped uterus even large doses, approximately one million M. U. of progynon B, only rather exceptionally will result in a noticeable increase of the uterus. However, the experience of Janson,²⁹³ using much larger doses, seemingly is quite different. In a twenty-one-year-old girl with a very small uterus and primary amenorrhea, the administration of a total of 26 million M. U. of progynon B led to gradual enlargement of the uterus until finally it had reached normal size. With cessation of the injections, there occurred one profuse hemorrhage lasting four days. Shortly afterward the woman married and became promptly pregnant. Kurzrok, Wilson, and Cassidy²⁹⁴ mention that they obtained noteworthy results in primary and secondary amenorrheas with relatively large doses, around and above 100,000 R. U. of progynon B.

In the light of available information, estrogenic follicular extracts can be useful in the treatment of amenorrhea only in two possible ways: In large doses by stimulating growth of an underdeveloped uterus, and in small doses by possibly inducing improved activity of the anterior pituitary gland.

The purpose of every reasonable treatment of amenorrhea obviously is initiation of regular ovulations, which are dependent upon an adequate and well-balanced supply of the two gonadotropic hormones of the anterior pituitary. Most commonly, therefore, at present are employed the anterior pituitary-like hormones from the urine of pregnant women. Once more we shall quote in this connection Emil Novak:²³⁰ Anterior pituitary-like substances are given because they show in animal experiments gonadotropic effects. For the human female, proportionately enormous quantities certainly would be required and even then we cannot justifiably expect a result, because the anterior pituitary-like substances used for this purpose are not produced by anterior pituitary glands but in the placenta. More will be said on this point later. Johnson²⁹⁵ injected four monkeys daily with 200 R. U. of antuitrin-S (a pregnancy urine extract) to a total dosage of from 2,400 to 2,800 R. U. but failed to produce any histologic evidence of increased

opsomenorrhœa (not mentioned in Stedman's medical dictionary, 13th edition) has been proposed for a menstruation in which the flows come periodically in long intervals. There can be no doubt that some individual instances of this condition in literature are recorded as "secondary" amenorrhœas. We may state in this connection that, as far as we know, no claim has ever been made for any kind of therapy to be successful in changing a long interval menstruation into one of the typical four weeks type.

The term *oligomenorrhœa* in gynecologic writings is indiscriminately employed to indicate either infrequent or scanty menstrual flows. (It is defined by Stedman as "scanty or infrequent menstruation," and by Dorland [17th edition] as "abnormally infrequent menstruation.")

The word *hypomenorrhœa* has been suggested and is in use to specify regular but scanty flows. (It is rather vaguely described by Stedman as "deficient menstruation" and by Dorland as "a deficient amount of menstrual discharge.")

Polymenorrhœa in both dictionaries is defined as "too frequent menstruation coming in shortened intervals."

We find the term *hypermenorrhœa* used to express excessive blood loss due either to profuse or to protracted flows. It seems practically identical to the commonly employed term *menorrhagia* which implies a certain regularity of the flow as distinguished from *metrorrhagia*, which always indicates irregularity.

The promiscuous use of these not any too well definable terms in gynecologic literature makes it impossible to present here any clear picture of views held in regard to either etiology or treatment of the various types of menstrual anomalies affecting either interval, duration, or intensity of menstrual flows.

We have previously spoken of the factors generally assumed to account for regularity in menstrual function. There might be a qualitative or quantitative disturbance in the output of either the follicle-stimulating or of the luteinizing hormone of the anterior lobe of the pituitary, but more commonly a shortened interval is ascribed to the quicker involution of a presumably smaller corpus luteum, and long intervals to the opposite condition.

Abnormally large blood loss, leading to secondary anemia, requires gynecologic attention. The first task is to determine whether the free menstrual flow is caused by any local pelvic anomaly, especially one within the genital organs, or represents merely a functional disorder. Obviously we can deal in this review only with the latter.

Intervals, too long or too short, and flows too scanty, too profuse, or too protracted, are most commonly seen at the age of puberty, before the required harmonious interaction of the various endocrine glands associated in normal menstruation has been fully established, and at the preclimacteric age, when the established equilibrium becomes disturbed through senile involution of the ovaries. Rongy, Tamis and Gordon³⁰⁵ write: Recent attempts to unravel the intricate mechanism of interglandular activity with particular reference to menstruation and its disorders have focused the attention of gynecologists on the functional disorders of the genital organs. It is now fairly well established that the disorders of menstruation in particular and of uterine bleeding in general may not have their origin in the genital tract but are often induced by an endocrine disturbance. It may be useful to quote here a

are decidedly more sensitive to overirradiation than is the pituitary. Among others they give the following conclusions: About one-half of the 47 amenorrheic and 15 oligomenorrheic women were seemingly cured. The procedure proved in their hands definitely harmless. Stoeckl³⁰⁰ refers to the commonly made claim, based on animal experiments, that these relatively small doses of x-ray could not possibly cause morphologic changes in the human hypophysis. He established the error of this claim. The death of a patient, thirty-eight days after administration of a total of only 610 r. to the pituitary region, gave him the opportunity to study the gland. He found about two-thirds of the anterior lobe necrosed. He mentions that in Vienna routinely only about 200 r. are given but that it would be impossible to deny that even this dose could cause histologic changes in the gland.

Merletti³⁰¹ claims to have cured many cases of amenorrhea by withdrawal of large quantities of blood by venesection. He feels that this method can well compete in effectiveness with organotherapy. He obtained particularly good results in amenorrhea due to psychic factors, which after all would not seem surprising.

In view of the previously mentioned rôle played by hyperactivity of the adrenal cortex in premature puberty, it was entirely logical for Neumann³⁰² to administer adrenal cortex extract to a woman suffering from Addison's disease, in whom the uterus had become atrophic and menstrual flows had stopped. He succeeded in restoring menstrual function.

Considering the present trend of using practically only hormone preparations in the attempt to restart menstruation, it seemed appropriate to Ripperger³⁰³ to remind us that there have been employed in the past many useful emmenagogues for the same purpose. He carefully surveys the long list, now almost forgotten and discarded with the exception of a few at present still in use but solely as abortifacients.

We shall close with a reference to a recent, comprehensive paper by Tschertok³⁰⁴ on the diagnosis and treatment of amenorrhea. Also he presents four graphic diagrams to show the interaction of various endocrines in relation to normal menstruation. He agrees with other writers that failures in hormone treatment often are due to insufficient analysis of type and cause of the condition in each individual case. He suggests the division of amenorrheas into the following 5 groups: (1) Changes in uterine mucosa with normal ovaries. In them there is no indication for hormone therapy. (2) Insufficient ovarian function with normal anterior pituitary activity. Administration of ovarian substances is indicated. (3) Insufficient anterior pituitary function. For this group he recommends alternating injections of anterior pituitary-like extracts and estrogenic substances. (4) Excessive activity of follicular apparatus. This cannot be influenced by hormone therapy. (5) Amenorrhea due to general causes. For them general hygienic-dietetic measures may be combined with organotherapy. His final conclusion is: Any schematic treatment for amenorrhea is useless and objectionable.

XIV. ANOMALIES OF INTERVALS AND OF MENSTRUAL BLOOD LOSS

This heading had to be selected for this chapter because there is at present no exact terminology available to express special forms of anomalies of interval or of amount of menstrual discharge. The term

will be a long-continued amenorrhea in spite of the hyperplastic endometrium. We must in this connection once more mention the already quoted paper of Stein and Leventhal²⁸⁶ in which they explain an amenorrhea in association with small cystic degenerated ovaries in quite a different manner as due to mechanical interference with the ovulation process. While they advocate partial resection of ovaries for the cure of amenorrhea, Robinson³⁰⁸ finds this same operation very useful for the cure of menorrhagia.

Burch and Burch³⁰⁹ showed that menorrhagias not necessarily arise only from a "Swiss cheese pattern" endometrium. They found that biopsies repeated on the same woman not so rarely reveal in some eyes a mucosa without any glandular dilatations and again in other eyes a typically hyperplastic endometrium. "In the final analysis endometrial hyperplasia is a disorder of the hypophyso-ovarian equilibrium."

Undue prolongation of the menstrual flow, according to Hirsh-Hoffmann,⁶⁹ is the result of delay in the extrusion of the menstrual endometrium because of deficient or incomplete involution of the corpus luteum. Schroeder³ dwells in detail on the relation of glandular cystic hypertrophy of the endometrium to disordered ovarian activity, a question also discussed by Tietze³¹⁰ and others.

Polycystic degeneration of the ovaries, in the belief of Kraul³¹¹ represents the morphologic expression of the fact that the equilibrium in hormone production has become disturbed. Clinically this is manifested in fluor, sterility but chiefly in anomalies of the menstrual flow. Out of 100 patients with small cystic degenerated ovaries 48 had an oligomenorrhea (no amenorrhea is mentioned), 46 a polymenorrhea, and only in 6 was the menstrual function approximately normal.

We already had occasion to refer to the doubt of various writers in the rather common assumption that scantiness or entire absence of menstrual flows always indicates a deficient ovarian activity. Since amenorrhea, oligomenorrhea, and functional bleeding of any sort, writes Anspach⁵⁴ are unreliable as positive indices of ovarian function, a test curettage is important as a diagnostic aid.

Elden³¹² emphasizes that there exists no definite relation of the particular type of menstrual disorder to any particular gland of the endocrine system. Haines and Mussey³¹³ discuss connections of amenorrhea, oligomenorrhea, and menorrhagia to a low basal metabolic rate in patients with thyroid hypofunction but free of any symptoms of myxedema. Their therapeutic results with thyroid preparations are noteworthy, and in the discussion of this paper Litzenberg fully supported their conclusions. Interruption of thyroid medication, in his experience, is usually followed by return of the previous menstrual disorder.

Systematic roentgenologic studies of the sella turcica convinced Bokelmann³¹⁴ not only of the value of this diagnostic method in judging sexual, functional disturbances in women, but as well forced him to the conclusion that in the interpretation of the various forms of hypogonitalism heretofore too much importance has been assigned to primary ovarian insufficiency. Practically identical are the conclusions of Fagioli³¹⁵ who emphasizes the frequency with which abnormally shaped and particularly large sellae turcicae are seen in women with disorders commonly ascribed to ovarian incompetence.

Haden and Singleton³¹⁶ found menorrhagias and metrorrhagias surprisingly common in women suffering from a simple achlorhydric, hypo-

few historical facts enumerated by Campbell, Lendrum and Sevringhaus.³⁰⁶ Hitschmann and Adler described the sequence of histologic changes in the endometrium, occurring during the menstrual cycle. When Kaufmann, Clauberg, and others were able to reproduce these changes by the administration of certain hormones, given in certain quantities and in a definite order, we were finally enabled to explain these morphologic changes in the terms of physiologic processes. Ample opportunity to study these changes in any given phase or even in all phases of one cycle was offered when methods were developed which made it possible to procure biopsy specimens with comparative ease and without noteworthy discomfort to the patient (by procedures which we have described previously in this review).

A specimen of endometrium procured at a known stage of the cycle permits certain conclusions in regard to the normal or disordered functional activity of the follicle or the corpus luteum. These points are made quite clear in a large series of microphotographs presented by Campbell and his coworkers. However, they feel forced to admit that it remains a fact that amenorrhea, cyclic follicular bleeding and menorrhagia of the endocrine type may be indistinguishable on the basis of endometrial histology.

For this reason the clinical course of the menstrual disorder and particularly certain hormone studies on blood and urine may be required for an exact diagnosis of the underlying cause. In regard to comparative studies of hormone levels in blood and urine, recent writers call attention to the possibility or fact that the transition of such hormones from blood to the urine necessarily depends on a certain renal threshold which possibly varies in the different phases of the cycle. It would be impossible to enter here in a discussion of this literature. We will give a quotation only from a paper of Sehuschania³⁰⁷ in which he speaks of the hormonologic and pathologic-anatomic pictures in cases of amenorrhea, metropathia hemorrhagica, and climacterium. In metropathia hemorrhagica, which undeniably is caused by an overproduction of follicular hormones, the follicular titer *in the urine* is below normal, probably because large quantities of the estrogenic substances are utilized in building up the hyperplastic endometrium. Siebke, just in these cases, has found high levels of estrogenic substances *in the circulating blood*. In cases of follicle persistence very little follicular hormone is present in the urine, while, on the other hand, large amounts of follicular hormone in the urine in cases of accelerated follicle ripening as a rule are seen associated with an atrophy and not with a hyperplastic endometrium.

An excess of follicular hormone thus can result in an hyperplastic endometrium which usually causes profuse or protracted menstrual flows but which at times entirely fails to pass through the secretory phase. This situation is described by Evans⁴⁰ as follows: Schroeder's disease, characterized by a hypertrophic endometrium and excessive bleeding, may be the result of a deficiency in gonadotropic hormones. Possibly only the luteinizing factor is deficient so that the effect of the other, the follicle-stimulating hormone, becomes relatively exaggerated. If under such conditions many follicles become cystic, they will actually pour out an excessive quantity of follicular, estrogenic hormone which will result in marked proliferation of the endometrium. In the absence of a sufficient supply of corpus luteum hormone, however, the result

completion of the "climacteric" period of transition which is characterized by varied manifestations of the pluriglandular reactions to the decline of ovarian function. In spite of this difference, the terms "menopause" and "climacterium" are usually employed synonymously. Therefore, among the symptoms of the menopause, outside of cessation of menstrual activity, commonly are included irregularity of flows, disturbances in the function of pituitary, thyroid, adrenal, and other glands, usually associated with a marked instability of the autonomic and particularly vasomotor system.

It seems that not sufficient emphasis is placed on the noteworthy fact that with normal, senile involution of ovarian activity the common general molimina often appear long before final cessation of menstrual flows, while in cases of operative or radiation castration usually some time elapses before these symptoms manifest themselves. An explanation for this difference may be found in the fact that in case of normal involution the balance between folliculin and progestin becomes gradually disturbed, while in artificial castration, certainly with removal of the ovaries both hormones are eliminated simultaneously. Women suffering from severe symptoms after natural climacterium often show large amounts of estrogenic substance in the urine. More recently also differences in the urinary levels of the two anterior pituitary-like hormones have been connected with certain symptoms, but views in this respect are not yet clearly enough defined to be quoted here. We know that partial or complete loss of ovarian function (Evans⁴⁰) leads to excretion of increased amounts of gonadotropic hormones in the urine, associated with morphologic changes in the pituitary gland, which can be reversed to normal (Clauberg and Breipohl²⁸⁹) by administration of either of the two ovarian hormones.

In contradiction to other investigators, Westman³²⁸ maintains that reactivation or rejuvenation of ovaries by means of gonadotropic hormones is possible. In two women, respectively fifty-one and forty-eight years old, both having passed through their menopause, he transfused intravenously, one week before required laparotomy, 225 and 400 c.c., respectively, of blood taken from pregnant patients near term. In the first woman, he found a follicular vesicle with partial luteinization of the granulosa cell membrane surrounded by small hemorrhages. In the other, there were present follicular vesicles in both ovaries with a markedly hyperemic granulosa membrane. Similarly Heimann,³²⁹ in experiments on guinea pigs, found that ovaries severely damaged with x-rays can be completely restored with administration of anterior pituitary hormones.

In regard to certain anomalies observed during the menopause, we will mention Maranon's³³⁰ assertion that hyperthyroidism, often evident in climacteric women, rarely is found associated with struma or exophthalmus. In the belief of Goldberg³³¹ acroparesthesia, a very common complaint of women in the menopause, has so far not been sufficiently investigated. He records good results with ovarian preparations. Pisk³³² finds that the various forms of neuralgia which develop during the menopause and often prove refractory to the usual antineuralgic treatment, may respond well to follicular hormone which he administers in daily doses of 200 M. U. Curschmann¹¹⁶ described two cases of climacteric edema. It is transient and possibly not rare, though it is presumably often erroneously ascribed to a cardiac or renal anomaly. For this

chronic anemia, which in literature also appears as chronic chlorosis or chlorotic anemia with achlorhydria. The disease responds almost specifically to iron therapy. With return of the blood picture to normal, the menstrual disturbance usually disappears promptly. Kuestner,¹⁸⁵ as already mentioned, believes that general endocrine activity and with it menstruation can become impaired by frequent or continued over-exposure to ultraviolet rays during sport activities. However, erythema doses of ultraviolet rays over the lower abdomen, diathermy, and simple heat applications, in the belief of Gillerson, Warschawer and Tykotschinskaja^{316a} are particularly useful because they stimulate the vegetative nervous system. Disturbances of the latter account for endocrine disorders which unfavorably affect the menstrual function. Infrared rays, on the other hand, according to Amstel³¹⁷ exert a most beneficial influence both on growth and sex hormones and for this reason are of great service in the treatment of amenorrhea, menorrhagia, vulvitis, pruritus, and krausosis vulvae. Lehmann³¹⁸ offers an exhaustive and critical analysis of the efficacy, in the treatment of ovarian insufficiency, of such physiotherapeutic methods as application of ultrared or ultraviolet rays, galvanic and high frequency currents, diathermy, short waves, massage, radium and x-rays. A paper of Francillon-Lobre³¹⁹ deals specifically with short wave therapy. In a large percentage of his cases, these waves resulted in disappearance of such disorders as amenorrhea, oligomenorrhea, and menopausal difficulties and incidentally also improved, as a rule, the patient's general health. In a statistical, clinical, experimental and therapeutic study of the effects of the seasons and of light on genital function, Kirchhoff³²⁰ arrives at the following conclusions: Exhaustive investigations of this cosmobiologic problem permit the deduction that light within certain wave-lengths definitely influences sexual hormone processes. This finding has practical significance so far as red light is concerned, which benefits markedly all hypohormonal disorders of women.

A method, years ago first recommended by German gynecologists, namely roentgenization of the spleen, in the experience of Vignali³²¹ proves particularly useful in the treatment of pubertal hemorrhages. Dogliotti³²² advocates for this same purpose repeated, small (10 c.c.) transfusions of blood. Holzapfel³²³ resurrects another old German therapeutic method known as athmocausis, consisting in the partial destruction of the endometrium by means of steam in cases of menorrhagia. Discussion of intrauterine application of radium for this purpose we leave for a later chapter.

Newer ergot preparations are extensively used for reducing menstrual blood loss. Among these, gynergen seemingly is enjoying particular popularity, and it, therefore, may be useful to mention a few reports of disagreeable by-effects of this preparation. Balcke³²⁴ saw gangrene of an extremity follow its use. The same accident is recorded by Cahill,³²⁵ and his report was promptly followed by one from Gould, Price, and Ginsberg³²⁶ who quote other such cases from the literature.

XV. MENOPAUSE

In the introductory remarks of a comprehensive survey of the symptoms and treatment of the menopause, Mazer and Israel³²⁷ point to the fact that generically the term "menopause" implies the physiologic cessation of the menstrual function. Actually menopause marks the

It seems superfluous to discuss here in detail the large and mostly controversial literature dealing with the relative values or advantages of roentgenization of but one ovary, hysterectomy, or intrauterine application of radium in the treatment of functional hemorrhages. The decision in each case must be made with consideration of many individual features as is so well shown in a paper of Keene and Payne.³⁴⁰

Experimenting on guinea pigs, Loeser³⁴¹ found that removal of the ovaries stimulates the output of the thyrotropic hormone of the anterior pituitary gland. In his belief, his good results in ameliorating the hyperthyroid symptoms of menopausal women with di-iodotyrosine are due to the fact that this drug reduces secretion of the thyrotropic hormone by the hypophyseal gland.

Fumarola³⁴² considers a belief in a specific climacteric neurosis unjustified. In most instances such a neurosis is only an incidental complication of the menopause. The few cases of seemingly true climacteric neurosis are really only particular forms of neurasthenia with exaggeration of vasomotor symptoms. But this form is characterized by its resistance to all forms of treatment and usually is only partially controlled by organotherapy.

Whittingdale³⁴³ justly stresses the necessity of a most careful examination, because many other coincident conditions or diseases can produce most confusing symptoms. He divides these patients roughly into two groups: the fat women, often with symptoms of arthritis, who must be reduced by diet and occasionally with thyroid, and the thin ones, who more often complain of insomnia, flushes, eructations, heart palpitation, etc. They usually require bromides, valerian, and other sedatives as well as a high calorie diet.

Bauer³⁴⁴ contributes a paper dealing specifically with the dietetic treatment of menopausal molimina. In general there is required restriction in proteins together with lessened physical activity. In instances of hypertension, a long-continued reduction of salt intake is important, often to be combined with reduction of protein intake. In stout individuals with hypercholesteremia, which is almost the rule in the combination of obesity with hypertension, all fats rich in lipoids must be avoided. In climacteric women with arthritic symptoms any excess of salt intake must be avoided. Hot flushes can be momentarily relieved by cold drinks, especially of effervescent waters. Crainicianu³⁴⁵ extols the value of calcium lactate which improves the tonus of sympathetic and vagus. He claims 86 per cent cures, 12 per cent improvement, and only 2 per cent failures in the treatment of all menopausal symptoms due to ovarian insufficiency. Bakaés³⁴⁶ finds calcium in combination with parathyroid most effective in controlling profuse flows; McFarlane³⁴⁷ finds emmenine useful for the relief of menopausal molimina.

In the belief of Aschner,³⁴⁸ the therapeutic results of gynecologic specialists in dealing with the menopausal woman are so unsatisfactory, because at this stage of life women are prone to develop anomalies which fall into almost every field of pathology. For this age, specialists in all branches of medicine record a higher incidence of glaucoma, cataract, iritis, scleritis, herpes, pruritus, eczema, arthritis, cardiac and renal disorders, neuralgias, emotional disturbances, etc. Naturally the symptoms of any of these diseases may be intensified or distorted in the presence of true menopausal molimina. Aschner agrees with Wiesel's contention that prevailing theories concerning the origin of these

reason alone, he emphasizes, it is of great clinical importance to know that a typical edema of menopause exists. In one of the cases the edema disappeared promptly and permanently with the use of progynon.

A specific hypertension of the climacteric woman is denied by many authors. Such women obviously are at an age when arterial and nephritic disturbances are relatively common. Different views have been expressed lately. Crainicianu and Jonesco³³³ claim climacteric hypertension to be a specific morbid entity, the result of predisposing factors (age, arteriosclerosis, and disturbed endocrine function) to which finally is added hyperactivity of the adrenal cortex due to elimination of ovarian function which normally acts as an inhibitor on the adrenals. In about one-half of such patients, they succeeded in lowering the high blood pressure by intravenous administration of folliculin. Schaefer³³⁴ reports substantial reduction of hypertension and amelioration of all accompanying symptoms with theelin in 13 menopausal women. But, on the other hand, we find Langeron³³⁵ contending that hypertension during the menopause is not necessarily caused by the latter, since in 21 per cent of such cases he could establish definitely other causes for the increased pressure. He found ovarian therapy of very little use in this condition. That this particular question cannot be considered as settled can easily be seen from a paper of Steinkamm and Giesen.³³⁶ In 35 women one intravenous injection of 200 M. U. of progynon almost typically lowered the blood pressure; a maximal depression of 25 mm. Hg was seen in menopausal women with marked vasomotor disturbances. However, using another 35 women as controls, they were able to ascertain that the identical effect can be obtained by making an intravenous injection of normal saline injection. In their own experience intramuscular injections of follicle hormone, even in large doses, never influenced an hypertension.

Emil Novak²³⁰ admits that we possess no definite information concerning the causation and nature of those curious phenomena of menopausal women, though they evidently are of vasomotor origin. Empirically we know that they follow elimination of ovarian activity and often are most troublesome when ovarian function apparently becomes deficient. Since complete cessation of ovarian function always induces hyperactivity of the anterior lobe of the hypophysis it seems plausible to ascribe the vasomotor disturbances to an excess of anterior pituitary hormones. Therefore, it seems logical to attempt an inhibition of anterior pituitary overactivity, at least in the premenopausal state, by means of estrogen substance.

Approximately on this basis, Collins, Thomas and Menville³³⁷ justify their recommendation of inhibiting anterior pituitary function by a large, inhibiting dose of x-rays directed toward the gland. They believe that such a dose has a destructive effect, thus prevents further production of prolactin. Histologic and hormonologic proof for such an effect, however, is still wanting. (See report on destructive effect of smaller doses by Stoeckl.³⁰⁰) Similar ideas are expressed by Asaturov³³⁸ who relieved partially or completely 27 menopausal women of all their discomforts by roentgenization of the hypophyseal region. According to Huet³³⁹ good effects occur even with dosages as low as 2,000 r. though usually 3,000 r. are required, given in 6 sittings, 500 r. each, applied through three fields.

with no chorionic villi. In gross appearance it was thinner and paler than placental tissue. The expulsion of decidual tissue spoke strongly for the presence of ectopic pregnancy. The irregular bleeding varied greatly in amount but usually was scant. It appeared only for a few hours and recurred at intervals varying from hours to days. Occasionally it was as much as a heavy menstrual flow but was rarely as severe as is seen in uterine abortion. This blood came from the uterine endometrium and not from the tubes. It probably commenced with the detachment or death of the embryo.

Pain was a constant symptom in this series, being present in every case; the severity varying with the extent of the gestation and whether or not there had been a rupture with intraabdominal hemorrhage. Before rupture there may have been all the physical signs of early pregnancy, including Jacquemier's sign, Cullen's sign, Hegar's sign, and enlargement of the uterus, which was usually not over the size of a two months' pregnancy. The gestational sac may have been so small that it was easily overlooked. In early examination for pregnancy one is not justified in too vigorously manipulating the adnexa to differentiate swellings, as the corpus luteum of pregnancy may be thus ruptured, or a loosely attached intrauterine pregnancy may be separated and an abortion started. Furthermore most women are too sensitive at this time.

Sudden pain in the lower abdomen was a very common symptom, being present in 84 per cent. This was localized on one side or the other in 48 per cent: on the right side in 20 per cent, and on the left side in 28 per cent. It was usually the first thing that led these women to consult a physician. This, as a rule, meant that there had been a tubal rupture. To us, rupture means that the gestational sac has broken through the wall of the tube in which it has been growing. It may break through the serosa into the abdominal cavity, associated with hemorrhage, or into the lumen of the tube. In the latter, less hemorrhage may result due to compression of the bleeding vessels with distention of the tube. The escape of the sac may eventually be through the fimbriated end. This is called a "tubal abortion." As the tubal peristaltic action forces the sac out of the tube, intermittent severe cramplike pains may be described. Fresh blood is a peritoneal irritant. Its escape into the abdominal cavity alone may cause severe pain. This may also produce the symptoms of syncope—faintness, pallor. With a considerable amount of blood escaping into the peritoneal cavity, besides the severe pain in the lower abdomen, there may be a shoulder pain, which is the result of irritation of blood between the liver and the diaphragm. The latter symptom was reported in 14 per cent. The pulse becomes rapid and thready and the skin clammy and perspira-

molimina, representing a combination of physiologic and pathologic phenomena, are unsatisfactory. These theories are not generally applicable, because the clinical picture in the individual case is always determined by certain constitutional factors. Therefore, Aschner,¹³⁰ in another paper, concludes that constitutional and not specific therapy offers the best chances, especially when dealing with neuroses or psychoses.

Also Sevringhaus²⁹¹ refers to the fact that climacteric disturbances often include periods of autonomic, emotional, and psychic instability which may last anywhere from a few days to nearly two decades in some instances. Hence, he reminds us, it always is difficult to make any statement that any particular therapy alters the duration of any symptoms, and especially so because there is never any control series available for the scientifically desirable test.

It seems appropriate to mention in this connection a paper read by Schneider.³⁴⁹ In it he reported excellent results obtained with estrogenic substances in the treatment of dysmenorrhea, secondary amenorrhea, menorrhagia, metrorrhagia, and sterility. In discussing this paper, Jean Paul Pratt recalled his very fine results reported ten years ago with small doses of follicular substance. With careful recheck later he was forced to the conclusion that they actually were most disappointing. At present he injects into patients referred to his department in the hospital for severe menopausal symptoms either a preparation of theelin in oil or the same kind of oil without any theelin. Just as much improvement has followed the one kind of injections as the other kind, though the results are not judged by him but by the referring physician who does not know whether the patient received theelin or simply pure oil.

This discussion of the medicinal treatment of climacteric discomfort we may well end with a reference to a fact known to all experienced practitioners: For the majority of worried, frightened, and emotionally disturbed women, premenopausal or postmenopausal, a quiet, encouraging, and occasionally reiterated explanation of the situation proves the most helpful and effective sedative.

The methods of possible prevention of disagreeable menopausal discomfort apply in general to operative measures.

Preservation of some ovarian tissue in the course of radical operations when necessary in relatively younger women is common practice. Unfavorable aftereffects of this conservatism, of course, are known.

Transplantation of ovarian tissue into other parts of the body is an old practice. Moure,³⁵⁰ using the method of Donay, transplants one ovary into one of the large labia. In discussing the favorable effect in his cases, he duly appreciates the merely psychic influence on the patients who are thus enabled to ascertain by palpation the presence of an ovary and to observe its functional activity by noticeable changes in its size. He feels that results could be greatly improved by an added transplantation of endometrial tissue into the cervical canal, so that also the bleeding phenomenon would be preserved. Transplantation of endometrial tissue into the cervix proved successful in preventing menopausal molimina in 8 cases reported by Fuchs.³⁵¹

Quite recently Solomons³⁵² described a case in which not only an ovary but also a piece of functioning endometrium was successfully transplanted from one woman to another. After years of amenorrhea

this woman again began to flow regularly. Stanea³⁵³ found that the maximal duration of life of an autotransplanted ovary in 120 cases amounted to thirty-nine months. Tonkes³⁵⁴ arrived at the conclusion that there is little sense these days to transplant an ovary in a case of supravaginal hysterectomy without simultaneous transplantation of endometrium. It seems that a functioning endometrium always preserves the ovary against degeneration.

In conclusion, we shall cite the ingenious operation devised by Strassmann⁸⁵ for overcoming amenorrhea in women in whom the uterine cavity for one reason or another has become atretic or obliterated, but who still possess functioning ovaries. Splitting the anterior uterine wall, he forms a channel into which he draws and sutures one tube. In 6 patients so operated upon, regular flows started and menopausal symptoms disappeared promptly. Somewhat optimistically, or humorously, Strassmann adds: "So far no pregnancy has been recorded." He speaks of this operation as a method of restoration of a functioning menstrual channel. Inevitably some discussion started among German writers whether these subsequent periodic flows can be justifiably called "menstruation" since they do not represent bleeding from an endometrium in its secretory phase. Correctly termed, they are pseudo-menstrual vicarious flows from the tubal mucosa.

XVI. SEXUAL HORMONES AND ORGANOTHERAPY

In the preceding chapters at the appropriate occasions mention has been made of the various hormone preparations now in common use. It seems, however, desirable to offer furthermore a brief survey of papers which deal rather with the general aspect of sexual hormonology and organotherapy.

Nielsen³⁵⁵ thinks that a revision of all theories concerning origin and activity of sexual hormones becomes necessary. Analyzing the chemical formulas of the various sex hormones, he shows that not only the male and female sex hormones but also the vitamins and cholesterol are built upon the carbohydrate radical $C_{17}H_{26}$. He concludes that there are not only three so-called sexual hormones but a whole series of substances, all closely related to each other, which without exceptions exert a stronger or weaker biologic effect. They are sterines, present in all organs, and any conception of specificity or of solely ovarian origin, e.g. of estrin, must be discarded. Estrin is present in large quantities in the urine of the male horse and is found in small amounts in the urine of human male. Only in analogy to known facts in regard to thyroxin, insulin, or adrenalin, the erroneous conclusion has been made that estrin is the product of the ovaries and androsterone that of the testicle. It would seem more logical to regard the sexual hormones solely as links in the chain of sterine metabolism.

Very similar are the views expressed by Windaus.³⁵⁶ He proves the close chemie connection between all these substances and shows that both male and female sex hormones fall into the chain of derivatives of cyclo-pentano-perhydro-phenatren. Seguy³⁵⁷ who reviews all available proofs that the characteristic follicular hormone certainly is not produced in the ovaries alone but is found in many other active cell tissues as a derivative of sterines, deals with this same question. Goldhammer and Loewe³⁵⁸ examined the urine of 64 men between the ages of nineteen and fifty-one years. In 32 perfectly normal men, the urine

of only 19 per cent gave a positive reaction for follicular hormone. In 32 other men, with certain anomalies of the vegetative nervous system, especially in regard to sexual function, this reaction was positive in 65.5 per cent.

In a very interesting paper, Seitz³⁵⁹ recently discussed the follicle hormone as a specific growth hormone, which during pregnancy, as a matter of fact, is produced by the chorionic tissue in large amounts together with anterior pituitary-like hormones and probably also a substance biologically identical with the corpus luteum hormone. Ehrhardt³⁶⁰ confirms previous findings that both the young and the ripe placenta contain corpus luteum hormone, seemingly in varying amounts.

Allen⁷ thinks that the close relation of chemical structures of follicular and luteal hormones, secreted by the same cells in different phases, suggests the possibility that progesterin may be formed by a change in the molecule of the estrogenic hormone. In the opinion of Marshall,³⁶¹ the reproductive hormones are metabolic by-products before they acquire hormone activities.

Nielsen, in his aforementioned paper, stated that only, when by means of artificial synthesis sufficient quantities of these various sterine derivatives will become available, we shall be enabled to make exact studies concerning their respective biologic effects, an essential desideratum for their intelligent administration in therapy. It seems that this goal has almost been reached.

Progesterone, the crystalline hormone of the corpus luteum, has been synthesized from stigmasterol, closely related to cholesterol, and from cholesterol by Tavaststerna.³⁶² Theelin in crystalline form has been produced from ergosterol, a plant sterol. Androsterone has been manufactured from cholesterol. Viosterol is obtained by irradiation of ergosterol with ultraviolet light.

Summarizing available information concerning the chemical structure of all these various substances, Ruzicka³⁶³ concludes that all of the sexual hormones can be considered as derived from cholesterol. They all contain a nucleus consisting of four carbon rings. The sex hormones differ from each other only in the side-chain arrangements around the common central nucleus.

Butenandt³⁶⁴ described the synthetic production of a presumably pure corpus luteum hormone either from stigmasterine (the sterine of the Soya bean) or from sterines extracted from the urine of pregnant women. Kaufmann¹³ tested the substance synthesized from stigmasterine on castrated women after having first produced endometrial proliferation by means of 300,000 M. U. of progynon. Six milligrams of this substance given daily for five days resulted in a menstruation-like flow. Biopsy showed the endometrium to be in the typical secretory phase. In Kaufmann's belief this experiment definitely proves that this chemical product is physiologically equivalent to the corpus luteum hormone.

Preisseker³⁶⁵ points out that a ready supply of corpus luteum preparation, at least theoretically, could be most useful: (1) In the production of pseudomenstrual flows in women without active ovaries; (2) in the prevention of certain types of abortion; (3) in amelioration of pain due to uterine spasticity (dysmenorrhea); (4) in the initiation of menstruation in cases of primary and secondary amenorrhea (after preceding stimulation with follicular hormone); (5) in influencing the duration of, and interval between, menstrual flows; (6) in correcting

elimaeteric disturbances, including menorrhagia; (7) in the cure of intermenstrual pain and bleeding; and (8) in the treatment of sterility.

Runge³⁶⁶ dwells on the possible importance of synthetic progesterone and particularly vitamins in the organotherapeutic armamentarium of the gynecologist.

Synthesized estrogen and progesterone, available in sufficient quantities and presumably then at a lower cost, will obviously limit present efforts of stimulating the production of these hormones in the patient's ovaries either by administration of gonadotropic, anterior pituitary-like substances or by irradiation of the pituitary gland for the purpose of increasing its output of gonadotropic hormones.

We had previously occasion to point out that the gonadotropic substances extracted from the urine of pregnant women in their biologic effects on testicles and ovaries are not identical with the gonadotropic hormones secreted by the anterior lobe of the pituitary (Schoekaert³⁶⁷). Siegmund³⁶⁸ suggests that the effect of anterior pituitary-like substances on the ovary depends upon the maturation stage of the follicle. Primordial follicles, even in adult individuals, do not react at all. Follicles of juvenile ovaries, when they contain a small amount of fluid, react the more promptly the further maturation has progressed. We also have referred in a preceding chapter to the theory that anterior pituitary-like hormones prove effective on the ovaries only when their influence "synergistically" is strengthened by substances simultaneously supplied by the hypophyseal gland. This view is not fully shared by Zondek.⁵

Accurate evaluation of clinical results with endocrine products as reported in the literature is practically impossible at the present state of wide discrepancies in standardization and in view of the failure of many writers to indicate dosage at least in specific unit terms. Thus in regard to the corpus luteum hormone, Corner¹⁰ states that the Clauberg unit represents about one-half of the potency of the Corner-Allen unit, though it is often asserted that it amounts to only one-fifth. In regard to standardization of estrogen-producing substances, a final solution has not yet been reached. Laqueur³⁶⁹ emphasizes the difficulties caused by the fact that reactions differ in different animals of the same species. He, therefore, suggests that all comparisons of strength be made solely with the preparations supplied by the Standardization Committee of the League of Nations. Schoeller, Dohrn, and Hohlweg³⁷⁰ consider even this procedure too inaccurate. Bourg³⁷¹ proposes an entirely new method of determining potency by testing the preparation in regard to its effect on the growth of the uterus of castrated rabbits. Coggi³⁷² recommends the use of the benzoate of folliculin which in animals shows an effect 30 per cent greater than that of the usual folliculin, and also in the human being gives better results. Its main advantage, however, is the possibility of determining exactly the required dosage by weight.

An Editorial in the London *Lancet* (2: 295, 1936) stressed the evident fact that sex hormone therapy could be put on a scientific basis only by general adoption of units of international validity. "It is quite impossible to compare accurately amounts expressed in mouse, rat, or rabbit units in published investigations from different laboratories or clinics."

Obviously therapeutic effects of the same preparation will differ under varying modes of administration. Only a small number of the marketed preparations, writes Biskind,³⁷³ are known to contain active material. Of the latter only very few, among them the estrogenic principle, are effective when administered by mouth. There is no satisfactory evidence that any of the pituitary preparations can be successfully given orally.

Only pure hormone products, stable and free of all toxic by-products, should be employed for subcutaneous injections. In this form they are decidedly more potent.

Urine of pregnant women has been used in form of enemas. Tachezy³⁷⁴ and Warschawsky,³⁷⁵ as well as Siegert, consider such rectal administration unesthetic but convenient, cheap, and useful. All the advocates of this form of application realize that such urine contains outside of anterior pituitary-like substances also other hormones and possibly toxic material. Some endocrinologists have and still employ (of course, without knowledge of the patient) disguised urine for oral use.

In relation to percutaneous administration, we must mention the claim of Vogt³⁷⁶ that applications of mud and mud baths are effective on account of the hormone contents of mud. We have previously spoken of application of anterior pituitary-like substances in form of salves by inunctions as recommended by Koschade.²⁴⁰ Zondek³⁷⁷ is convinced that the estrogenic principles are effective in oral, rectal, subcutaneous, and percutaneous administration. The last mentioned exhibits definite local effect, and for this reason is particularly valuable in the treatment of certain forms of pruritus vulvae or acne. He does not refer to local use in cases of senile vaginitis, but it would seem logical to make experiments in this respect.

Unique is Stanca's³⁷⁸ administration of ovarian extract by means of direct injection into the ovary. In a nineteen-year-old girl with primary amenorrhea, suffering from very frequent epileptic attacks, he injected during a required laparotomy 1 c.c. of ovarian extract into each ovary. Within twelve days the first menstrual flow appeared. After three more flows the patient became pregnant. When seen two and one-half years later, the patient was still menstruating regularly and had had no epileptic attack since operation. Stanca feels that intraovarian injection of folliculin may have its own specific effect.

Much interest has been shown in the immediate fate of therapeutically administered hormone substances. According to Silberstein, Molnar and Engle,³⁷⁹ injected follicular hormone, in experiments on dogs, was rendered inactive within two hours by the circulating blood and the liver. Studies made by Robson, Mac Gregor and others³⁸⁰ indicate that the human body rapidly destroys, makes inactive or eliminates administered estrogenic hormone. For instance, four hours after injection of 10,000 M. U. the blood contained less than 25 M. U. per liter. Zondek's³⁸¹ findings were as follows: After oral or subcutaneous administration of folliculin (hormone) only very small amounts can be recovered in active form from the urine. A woman, forty-five years old, receiving over 500,000 M. U. eliminated in the urine only 3 per cent. That the administered hormone becomes inactivated within the body, in his belief, is proved by the fact that it can be reactivated by hydrolysis. The inactivation seemingly takes place in the liver under the influence of ferments; however, the benzoate form of the ovarian hormone is not inactivated in this manner.

Rather conflicting views are expressed concerning undesirable and unexpected by-effects of potent hormone preparations when administered either in large doses or for a long time. Baehman, Collip, and Selye³⁸² reported that in adult rats daily injections of anterior pituitary-like substances, when continued for long periods, resulted in the production of a definitely antigonadotropic substance in the blood. Emil Novak²³⁰ speaks of this finding as the "bedeviling concept of an anti-hormone" developing under continued hormone introduction, and hopes that it will not be found true for theelin. He must have felt pleased to see the assertion of D'Amour, Dumont, and Gustavson³⁸³ that their investigation failed to ascertain the formation of antihormones under administration of estrin. They suggest that Collip's antihormone possibly is only an antibody developed under the effect of protein substances contained in the injected preparations.

More or less emphatic warnings against reckless use of potent hormone products mostly refer to follicular substances. This possibly is due to the fact that the estrogenic principle among all sex hormones was the first to become available in high concentration and thus is the one in greatest and longest use.

Any direct harmful effect of theelin or similar preparations on the ovaries is denied by Allen and Diddle,³⁸⁴ Busehbeek²³⁵ and others, which is not surprising since, as a rule, an endocrine gland is not affected by its own hormone extract. Nevertheless we find Mazer, Meranze, and Israel³⁸⁵ making the following statement: Doses relatively much larger than those employed clinically did not produce macroscopic or microscopic changes in any of the vital organs of rabbits. The response of the ovaries to very large doses is either degenerative or stimulating, dependent upon species and age of the animals and upon the duration of administration.

Estrogen administration certainly affects pituitary function and thus indirectly ovarian activity. Without going here into details or repeating what already has been said in this respect in preceding chapters, we shall quote but a few authors. Clauberg and Breipohl²⁸⁹ definitely showed that continued large doses of follicular hormone suppress the output of gonadotropic hormones by the hypophysis and that this function is restored to its previous level immediately after cessation of further administration of folliculin. Observations made by Frank and Salmon²⁹⁰ established that progynon B causes prompt reduction and within twenty-eight to eighty days complete disappearance of the anterior pituitary-like substances in the urine of menopausal women. Discontinuation of progynon at once is followed by reappearance of these substances in the urine. Identical findings are reported by Jones and Mac Gregor²⁸⁶ who experimented on 10 women at ages between fifty-two and eighty-three years. Noteworthy to the clinician, however, would seem the fact that in 7 of these 10 old women uterine bleeding started. Mazer and others,³⁸⁵ in a clinical study, ascertained that a total of 100,000 to 200,000 R.U. of estrogenic substance, given to patients in divided doses over periods of two to three months, produced no appreciable changes in body weight, basal metabolism, blood pressure, blood counts, coagulation and bleeding time, blood chemistry and urine. However, in 6 out of 17 regularly menstruating women such large quantities of follicular hormone produced delay of menstrual flows from one to three weeks "apparently as result of an inhibitory effect on the anterior lobe of the pituitary."

Very important information concerning this functional impairment of the hypophysis has recently been furnished by Zondek.³⁸⁷ Injections of folliculin can reactivate the ovaries of a senile mouse, so that estrus again will occur regularly. This fact can be explained only by restoration of discontinued or weakened gonadotropic function of the anterior pituitary lobe. Other experiments were made by Zondek on rats and chickens to ascertain the effect of continued administration of follicular hormone in moderate doses. Prolonged administration definitely interferes with anterior pituitary function, but this effect does not manifest itself either equally or simultaneously on all the various hypophyseal hormones. The output of the gonadotropic principles seems most sensitive and therefore atrophy of the genitalia in rats appears as the first result. The ovaries become so small that they cannot be identified with the naked eye. They may contain a few, very small follicles but never corpora lutea. The effect on birds seems to be identical. Next affected is the growth hormone. Pituitary gland and adrenals, however, become enlarged. If the follicular treatment is discontinued after several months, the animals do not spontaneously resume growth, which however promptly starts with administration of Evans' pituitary growth hormone. Zondek gained the impression that administration of follicular hormones actually stimulates the production of other hypophyseal hormones, e.g. the thyrotropic and parathyrotropic.

In similar experiments on 10 old women, Jones and Mac Gregor³⁸⁸ found that estrogenic substances do not inhibit production of the diabetogenic hormone of the anterior pituitary lobe.

Not so rarely writers mention marked increase in libido as undesirable by-effect of folliculin treatment. Obviously this effect is particularly inconvenient in young children and old women. Since the introduction of theelin by Lewis³⁸⁹ for the treatment of gonorrhea in children, authors repeatedly have referred to enlargement, at times painful, of the breasts, slight bloody discharges or aroused libido as occasional drawbacks in this therapy.

Zuckermann and Morse³⁸⁹ assert that large doses of estrin can lead to excessive hyperplasia of the endometrium with extensive necrosis of the superficial layers and cyst formation in the deeper layers.

It would lead us too far to quote literature discussing the rôle possibly played by excess amounts of estrogen in structural changes of the cervix suggesting malignancy or in the etiology of myomatosis or endometriosis. Cesa³⁹⁰ describes such intense changes in the cervix following large doses or prolonged administration of estrogenic material. Incidentally he also asserts that these alterations again disappear under the influence of corpus luteum hormone.

On better evidence rests a belief in possibly harmful effects of excessive doses of folliculin on the breasts. We have already spoken of the studies of Taylor¹³⁵ concerning the relation of chronic mastitis to certain hormones of the ovary and pituitary. Mac Donald,³⁹¹ on the basis of experimental investigations, denies that either estrin or progesterin could produce specific pathologic lesions such as cystic disease or adenosis of the mammary glands. However, very recently, Herold and Effkemann³⁹² came to opposite conclusions. They found that administration of follicular hormone for only a limited time, in adult female rats, results in the appearance of cyst formations arising from either acini or milk ducts. In their opinion, this effect is very similar, if not identical, to the glandular cystic hypertrophy of the endometrium so

characteristic for an increased supply of follicular hormone. Other investigations made by them, in their belief, strongly suggest that in the genesis of fibrosis mammae cystica of women a continuous excess of this hormone plays a significant part.

At the 1936 meeting of the American Gynecological Society, Emge expressed justifiable doubt whether it is safe to administer large doses of potent hormonal substances over long periods of time without the possible risk of awakening to activity dormant carcinomorphic elements. In a recent meeting of German gynecologists one speaker, referring to the striking chemical similarity of hormone to carcinogenic substances, warned that indiscriminate use of such preparations at the present state of our information might well be contrary to the principle, sacred to every physician "*Nihil nocere.*"

Some justification for extreme caution can be found in the possibility, if not likelihood, of damage to germ plasma as the result of endocrine therapy. Wolff³³³ has definitely established such permanent damage for the white mouse. Therapeutic administration of prolactin can lead to the production of defective ova as result of precipitated follicle maturation. Quite recently (in 1937) Wolff published further observations made on the human female, and concluded that prolactin should not be given to women still in the childbearing age and particularly not in cases of amenorrhea when anterior pituitary-like substances often are used in large doses in the attempt to induce ovulation for the purpose of restoring fertility.

We will simply list a few of the authors who estimate in comprehensive form the value of marketed preparations for the treatment of the various disorders of the menstrual function: Benthin,²⁷⁹ Biskind,³⁷³ Frank,²¹ Kaufmann,²³² Meigs,²⁴¹ Neumann,³⁹⁴ Emil Novak,²³⁰ and Josef Novak,²⁸¹ this last mentioned writer concluding his summary with the statement: "Very much is still in complete darkness. Within the next few years, however, we probably shall learn many new facts and will have to forget much of the present." Many others of these summaries sound not any less skeptical.

In conclusion, it seems well worth while to repeat a few of the comments made in an Editorial of the Journal of the American Medical Association of Oct. 24, 1936:

In order not to be outdone by a colleague, physicians demand the hormones (from the manufacturers) as rapidly as they can be separated from the tissues, blood, or excreta of animals or man, and proceed to inject them into patients.

A disturbing feature is that the medical literature is being filled with articles which are almost unanimously enthusiastic and which often give evidence of lack of critical consideration.

It is difficult to find articles recording failures. One never sees in print, e.g. a report of an experience like that of an endocrinologist who injected an extract into a fifteen-year-old girl for dysmenorrhea. The size of the ovaries seemed normal before the injections were given. At the conclusion of the treatment, an acute appendicitis developed and at operation the surgeon found bilateral cystic ovaries the size of oranges.

For the present only those clinicians with facilities for critical study should be encouraged to administer the newer endocrine preparations to patients, and these clinicians should be urged to publish their negative results as well as their positive results.

A large group of physicians should cease their indiscriminate injections of unknown substances into unsuspecting patients.

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3720 WASHINGTON BOULEVARD

Correspondence

To the Editor:

More than ten years have passed since obstetricians have adopted the combination of extracts of the thymus gland and the posterior lobe of the pituitary ("thymophysin"), suggested by me as an agent in labor for use in the stage of dilatation. Every opinion and every method has its followers and its opponents. This applies also to thymophysin.

One can easily understand and appreciate these facts with regard to any remedy. However, certain imputations raised against thymophysin accusing the combination to be "an unscientific preparation marketed under false claims" are so serious that they are inconsistent not only with my scientific reputation but also with facts which are supported by a majority of opinions in favor of this oxytocic.

He who quotes publications based upon a few cases as proof for the usefulness or uselessness of a new method must put himself into an untenable position. But if a material is collected from the literature based upon more than 100,000 deliveries reported by well-known clinicians; if a series of publications and theses from well-known university clinics are on record, and if, finally, equally distinguished professors of obstetrics summarize their unanimous judgment on thymophysin, that this preparation represents a distinct progress in the therapeutic armamentarium of the obstetrician, then these facts should be considered evidence of its value.

More than 100 papers dealing with thymophysin have been published in acceptable medical journals.

These judgments, at any rate, together with extensive evidence furnished in the reports of other observers, may induce the obstetricians of the United States, to whose scientific judgment I attach special importance, themselves to test the combination of extracts of the thymus gland and the posterior lobe of the pituitary in a larger number of deliveries.

MIKLOS TEMESVARY, M.D.

Buda-Pesth,
August, 1937.

NOTE: An extensive bibliography dealing with the employment of this preparation and appended to the above communication, cannot be included for lack of space.

EDITOR.

tion marked. Consciousness may be lost. Even without marked blood loss tenderness of the lower abdomen and rigidity are frequent. Tenderness was present in 93 per cent of these women and was localized on the left side in 27 per cent and on the right side in 38 per cent, being on both sides in 28 per cent. Nausea and vomiting were also common, being present in 44 per cent of this series.

It is rare that patients succumb from the first attack of sudden pain. There may be several attacks before the physician is called.

Pelvic findings may be very misleading, even if one is able to make a satisfactory examination. Usually when a woman is in much pain this is not possible. A mass was found in only 56 per cent of these hundred women. It could be defined as on the left side in 20 and the right in 20 and in the posterior culdesae in 16. When the pregnancy was early, as was usually the case, the swelling was so small as to be confused in size and location with an ovary. A fresh blood clot may be pressed into by the examining fingers and go unrecognized, especially under anesthesia. When the blood clot becomes organized it is more readily palpable.

The most important laboratory finding was the leucocyte count. In this series 77.5 per cent of the cases showed a count higher than 10,000. It is an accepted fact that leucocytosis appears with intraabdominal hemorrhage. If repeated counts are taken on an individual, it will be found that great variation develops from day to day or from hour to hour. It would seem that after the blood becomes organized there is less "insult" to the peritoneum and the count will drop to normal. With new bleeding it will rise again.

The diagnosis of ectopic pregnancy, we feel, then is most difficult before rupture. Since the last series was written, the Aschheim-Zondek test has come into use and has been of aid in making a definite early diagnosis of pregnancy. With rupture and its typical symptoms, diagnosis should be comparatively easy. However, when not seen until some time after rupture, the acute symptoms may have subsided; a slight fever may develop and the leucocyte count may be nearly normal; the severe pain becomes a dull ache; syncope and pallor have disappeared. The picture now resembles pelvic inflammation. The palpable mass can be confused with an inflammatory process. Here again the Aschheim-Zondek test is of help and a chronologic history of events should be carefully studied. The pregnancy may have aborted through the tube and the bleeding ceased spontaneously. One of several things may follow: profuse hemorrhage, shock, and death; operation with recovery or the products of conception be completely absorbed, or the ovum find a new site for attachment and continue to grow as an abdominal pregnancy.

British College of Obstetricians and Gynecologists

At a convocation held in the "College House" in London, on October 22, 1937, Dr. George Gray Ward, of New York, Emeritus Professor of Obstetrics and Gynecology of Cornell University and Chief Surgeon of the Woman's Hospital, was inducted as an Honorary Fellow of this English institution. This distinction has been conferred previously upon American physicians in only two instances, on Dr. J. Whitridge Williams, of Baltimore, in 1931, and Dr. William P. Graves, of Boston, in 1932.

American Board of Obstetrics and Gynecology

The next examinations (written and review of case histories) for Group B candidates will be held in various cities of the United States and Canada on Saturday, November 6, 1937, and Saturday, February 5, 1938. Application for admission to these examinations must be filed on an official application form in the office of the Secretary at least sixty days prior to these dates.

The general oral, clinical and pathological examinations for all candidates (Groups A and B) will be conducted by the entire Board, meeting in San Francisco, California, on June 13 and 14, 1938, immediately prior to the meeting of the American Medical Association.

Application for admission to Group A examinations must be on file in the Secretary's Office before April 1, 1938.

For further information and application blanks address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh (6), Pa.

Central Association of Obstetricians and Gynecologists

The Ninth Annual Meeting of the Central Association of Obstetricians and Gynecologists was held at the Hotel Adolphus in Dallas, Texas, October 14 to 17, in connection with a meeting of the Texas Association of Obstetricians and Gynecologists. Dr. John A. Kolmer, of Philadelphia, was the guest speaker of the Texas Association and Dr. C. Macfie Campbell, of Cambridge, Mass., was the guest speaker of the Central Association.

Minneapolis has been chosen as the meeting place in 1938, and the Officers and Executive Committee personnel for the coming year are as follows: *President*, Robert D. Mussey; *President-Elect*, Ralph A. Reis; *Vice-President*, William T. Black; *Secretary-Treasurer*, William F. Mengert; *Assistant Secretary*, Earl C. Sage.

Books Received

CHILDREN HANDICAPPED BY CEREBRAL PALSY. Psychological factors in management. By Elizabeth Evans Lord, Ph.D., psychologist to Children's Hospital, Boston, etc. With a medical explanation by Bronson Crothers, M.D. The Commonwealth Fund, New York, 1937.

MEDIKAMENTOESE BEKAEMPFUNG DER INTRAUTERINEN ASPHYXIE. Von Dr. med. habil. H. Nevinny, Universitaets-Frauenklinik, Koenigsberg. Mit 48 Textabbildungen, 104 Seiten. Ferdinand Enke, Stuttgart, 1937.

EMOTIONAL ADJUSTMENT IN MARRIAGE. By Le Mon Clark, M.D., assistant in obstetrics and gynecology, University of Illinois College of Medicine. 261 pages. The C. V. Mosby Company, St. Louis, 1937.

THERAPIE DER FRAUENKRANKHEITEN. Von Professor Dr. W. Benthin, Koenigsberg i.P. Zweite, neubearbeitete Auflage. Mit 23 Abbildungen im Text, 210 Seiten. Urban & Schwarzenberg, Berlin und Wien, 1937.

MATERNAL CARE. The Principles of Antepartum, Intrapartum, and Postpartum Care for the Practitioner of Obstetrics. Approved by the Committee on Maternal Welfare, Inc. Dr. Fred L. Adair, Editor. The University of Chicago Press, Chicago, Ill.

THE ENDOCRINES IN OBSTETRICS AND GYNECOLOGY. By Raphael Kurzrok, Ph.D., M.D., associate in obstetrics and gynecology, College of Physicians and Surgeons, Columbia University. Illustrated, 488 pages. Williams and Wilkins Company, Baltimore, 1937.

GETTING READY TO BE A MOTHER. By Carolyn Conant van Blarcom, R.N. Third edition, revised. With 97 illustrations, 305 pages. The Macmillan Company, New York, 1937.

TEXTBOOK OF SURGICAL NURSING. By Henry S. Brookes, Jr., M.D., instructor in clinical surgery, Washington University School of Medicine, etc. With 233 illustrations, 636 pages. The C. V. Mosby Company, St. Louis, 1937.

OBSTETRIC AND GYNECOLOGIC NURSING. By Frederick H. Falls, M.D., professor of obstetrics and gynecology, University of Illinois, College of Medicine, etc., and Jane R. McLaughlin, supervisor of the Department of Obstetrics and Gynecology, Research and Educational Hospital, etc. With 83 illustrations, 492 pages. The C. V. Mosby Company, St. Louis, 1937.

SYNOPSIS OF GYNECOLOGY. By Harry Sturgeon Crossen, professor emeritus of clinical gynecology, Washington University School of Medicine, etc., and Robert James Crossen, assistant professor of clinical gynecology and obstetrics, Washington University School of Medicine, etc. Second edition. With 106 illustrations, 247 pages. The C. V. Mosby Company, St. Louis, 1937.

LIGHT THERAPY. By Frank Hammond Krusen, associate professor of Physical Medicine, The Mayo Foundation, University of Minnesota, etc. Second edition, revised and enlarged. With 42 illustrations, 238 pages. Paul B. Hoeber, Inc., New York, 1937.

Items

Pittsburgh Obstetrical and Gynecological Society

At a regular meeting of the Pittsburgh Obstetrical and Gynecological Society held on October 11, the following officers were installed: President, Dr. Paul Titus, Vice-President, Dr. S. A. Chalfant.

- FITZGERALD, JAMES E., (WITH BREWER, JOHN I.), Six normal and complete presomite human ova, 210
- FRANKENTHAL, LESTER E., JR., (WITH KOBAK, ALFRED J.), Treatment of cervicovaginitis in children with silver picrate suppositories, 292
- FRAZELL, E. L., (WITH HEALY, WILLIAM P.), Method and results of treatment in carcinoma of cervix at Memorial Hospital, 593

G

- GAINES, JOSEPH A., Massive puberty hypertrophy of breasts, 130
- GOLDSCHMIDT, SIEGFRIED, (WITH DRABKIN, CHARLES), Chemical determination of pregnancy by Vischer-Bowman technique, 634
- GOODALL, J. R., AND POWER, R. M. H., Modification of Le Fort operation for increasing its scope, 968
- GOUGH, JAMES A., Aberrant suprarenal gland tissue in broad ligament, 1040
- , Study of five patients with chorionepithelioma, 267
- GRAD, HERMANN, Bissell operation for cystocele, 589
- GRIER, ROBERT M., Maternal morbidity, 298
- , Study of 100 consecutive cases of ectopic pregnancy, 103
- GRIMSON, MOZELLE, (WITH FINOLA, GEORGE C., AND TRUMP, RUTH A.), Bone changes in fetus following administration of dicalcium-phosphate and viosterol to pregnant mother, 955
- GUTTMACHER, ALAN F., Analysis of 521 cases of twin pregnancy, 76

H

- HAMILTON, BUFORD G., Fear, 183
- HARDEN, BOYD, (WITH HUGGINS, RALEIGH R., AND COHEN, MORTIMER), True hermaphroditism in man with an endocrinologic study, 136
- HARLOR, D. M., (WITH COLLETT, MARY E. ET AL.), Effect of estrin upon basal metabolism rate and nervous symptoms of ovariectomized women, 639
- HARRAR, JAMES A., Worth-while surgery in newborn, 661
- HAUPTMAN, H., (WITH ROYSTON, G. D., AND JENSEN, JULIUS), Tuberculosis and pregnancy, 284
- HEALY, WILLIAM P., AND FRAZELL, E. L., Methods and results of treatment in carcinoma of cervix at Memorial Hospital, 593
- HELLMAN, ALFRED M., AND MUSA, GEORGE, Studies on dried blood serum of women, 656
- HESELDTINE, H. CLOSE, Biologic and clinical import of vulvovaginal mycoses, 855
- , Experimental and clinical therapy of vulvovaginal mycoses, 439
- HOROWITZ, EDWARD A., (WITH BIERMAN, WILLIAM), Gonorrhea in female treated by combined heating technique, 68
- HUGGINS, RALEIGH R., COHEN, MORTIMER, AND HARDEN, BOYD, True hermaphroditism in man, with an endocrinologic study, 136
- HUNNER, GUY L., Unusual obstetric injury causing detachment of bladder and urethra from symphysis pubis and complete epispadias, 810

- HUNT, ARTHUR B., AND MUSSEY, ROBERT D., Delivery following stillbirth from dystocia in previous pregnancies, 310

I

- INGRAHAM, HAROLD C., AND ROSEN, JAMES . ALAN, Obstetric analgesia with acid alurate in rectal ether oil, 672
- IRVING, FREDERICK C., Conservative treatment of premature separation of normally implanted placenta, 881

J

- JAMES, H. C., Unilateral gonorrheal salpingitis in bicornuate uterus, 1045
- JAVERT, CARL T., Erythroblastosis fetalis as a cause of infantile mortality, 1042
- JENSEN, JULIUS, (WITH ROYSTON, G. D., AND HAUPTMAN, H.), Tuberculosis and pregnancy, 284

K

- KANTER, A. E., Ovarian pregnancy, 1035
- KAPLAN, IRA I., Sterilization by irradiation, 507
- , Study of end-results of treatment of amenorrhea and sterility by radiation of 128 married women over a period of 12 years, 420
- KEENE, FLOYD E., AND PAYNE, FRANKLIN L., Treatment of functional uterine hemorrhage, 688
- KENNEDY, FOSTER, Sterilization and eugenics, 519
- KENNEDY, WILLIAM T., Incontinence of urine in female, urethral sphincter mechanism, damage of function, and restoration of control, 576
- KLEMPNER, EMANUEL, Ureterohydronephrosis resulting from pelvic inflammatory disease, 125
- KOBAK, ALFRED J., AND FRANKENTHAL, LESTER E., JR., Treatment of cervicovaginitis in children with silver picrate suppositories, 292
- KOFF, ARTHUR K., AND DAVIS, M. EDWARD, Mechanism of prolongation of pregnancy in rabbit, 26
- KOMAROMY, GEZA G., Tetanus associated with criminal abortion, 687
- KOPP, MARIE E., Eugenic sterilization laws in Europe, 499
- KOTZ, JACOB, AND PARKER, ELIZABETH, Primary dysmenorrhea—an endocrine problem, 38
- KRIGBAUM, ROY E., An aid in study of sterility, 1046
- KROHN, LEON, LACKNER, JULIUS E., AND SOSKIN, SAMUEL, Effect of ovarian hormones on human (nonpuerperal) uterus, 379
- , (WITH LACKNER, JULIUS E., AND SOSKIN, SAMUEL), Etiology and treatment of primary dysmenorrhea, 248

L

- LABATE, JOHN S., AND REYNOLDS, SAMUEL R. M., Sensory pathways of ovarian plexus, 1
- LACKNER, JULIUS E., KROHN, LEON, AND SOSKIN, SAMUEL, Etiology and treatment of primary dysmenorrhea, 248
- , (WITH KROHN, LEON, AND SOSKIN, SAMUEL), Effect of ovarian hormones on human (nonpuerperal) uterus, 379

INDEX TO VOLUME 34

AUTHORS INDEX*

A

- ADAIR, FRED L., AND WATTS, RUTH M., Study of hormonal content of ovarian cyst fluids, 799
- ANDERSON, DAVID FYFE, (WITH NOVAK, EMIL), Sarcoma of uterus, 740
- ANDERSON, MILFORD X., AND SHIELDON, EVERETT A., Granulosa cell carcinoma of ovary in child of three years and nine months, 119
- ARMSTRONG, MERVYN V., Angiomatosis retinae (Von Hippel's disease, Lindau's disease) complicated by pregnancy, 494

B

- BAER, JOSEPH L., REIS, RALPH A., AND LAENLE, ROBERT M., Prolapse of uterus—shifting trends in treatment, 827
- BEHM, KARL H., (WITH TRITSCH, JOHN E.), Clinical experience with a new ergot alkaloid, 676
- BERKOW, SAMUEL GORDON, Status of biometry in endocrine diagnosis, 114
- BIERMAN, WILLIAM, AND HOROWITZ, EDWARD A., Gonorrhea in female treated by combined heating technique, 68
- BILL, ARTHUR H., Analgesia and anesthesia and their bearing upon problem of shortened labor, 868
- BISHOP, ELIOT, Operative methods of sterilization in female, 505
- BLAKELY, STUART B., Diagnosis of sex of human fetus in utero, 322
- BREWER, JOHN I., AND FITZGERALD, JAMES E., Six normal and complete presomite human ova, 210
- BROWN, WILLIS (WITH MILLER, NORMAN F.), Surgical treatment of complete perineal tears in female, 196
- BRUNER, J. M., ROSEBROOK, L. E., AND CUSHMAN, G. W., Photographic records of cervix uteri, 1027
- BUBIS, J. L., Retrograde cystocele operation, 225
- BUTTERWORTH, J. S., (WITH TRAUT, HERBERT F.), Theca, granulosa, lutein cell tumors of human ovary and similar tumors of mouse's ovary, 987

C

- CHEATHAM, GOODE R., Ateleetasis as a complication of obstetric analgesia, 166
- CLINTON, W. R., (WITH SIDDALL, R. S.), Lymphangioma of ovary, 306
- COHEN, MORTIMER, (WITH HUGGINS, RALEIGH R., AND HARDEN, BOYD), True hermaphroditism in man with an endocrinologic study, 136

- COLLETT, MARY E., SMITH, JOSEPH T., WERTENBERGER, GRACE E., HARLOR, D. M., REEO, FAITH W., AND LONG, SARA J., Effect of estrin upon basal metabolism rate and nervous symptoms of ovariectomized women, 639
- COMPTON, BEVERLEY C., Malignancy of granulosa cell tumors, 85
- COSGROVE, S. A., Surgical complications of pregnancy, 469
- CRABTREE, E. GRANVILLE, PRATHER, GEORGE C., AND PRIEN, EDWIN L., End-results of urinary tract infections associated with pregnancy, 405
- CUSHMAN, G. W., (WITH BRUNER, J. M., AND ROSEBROOK, L. E.), Photographic records of cervix uteri, 1027

D

- DANFORTH, W. C., Carcinoma of cervix during pregnancy, 365
- DAVIS, M. EDWARD, (WITH KOFF, ARTHUR K.), Mechanism of prolongation of pregnancy in rabbit, 26
- DECOSTA, EDWIN J., AND REIS, RALPH A., Oral administration of paraldehyde for relief of pain during labor, 448
- DE SNOO, K., Prevention of eclampsia, 911
- DOUGLAS, R. GORDON, Hypertension, nephritis, and toxemias of pregnancy, 565
- DOUGLASS, MARION, (WITH FALLON, F. S.), A new type of syringe adapted for treatment of endocervicitis, 170
- DRAKIN, CHARLES, AND GOLDSCHMIDT, SIEGFRIED, Chemical determination of pregnancy by Visseher-Bowman technique, 634

E

- EASTMAN, NICHOLSON J., Vascular factor in toxemias of late pregnancy, 549
- EHRENFEST, HUGO, Menstruation and its disorders, 530, 699, 1051

F

- FALLON, F. G., AND DOUGLASS, MARION, A new type of syringe adapted for treatment of endocervicitis, 170
- FALLS, FREDERICK H., Actinomyces of ovary, 1033
- FINOLA, GEORGE C., TRUMP, RUTH A., AND GRIMSON, MOZELLE, Bone changes in fetus following administration of diacalcium-phosphate and viosterol to pregnant mother, 955

*July, pp. 1-182; August, pp. 183-364; September, pp. 365-548; October, pp. 549-730; November, pp. 731-910; December, pp. 911-1022.

- SMITH, FRANK R., Effect of pregnancy on malignant tumors, 616
- SMITH, JOSEPH T., (WITH COLLETT, MARY E. ET AL.), Effect of estrin upon basal metabolism rate and nervous symptoms of ovariectomized women, 639
- SMYTHE, FRANK WARD, Ten-year statistical report of carcinomas of cervix, 317
- SOSKIN, SAMUEL (WITH KROHN, LEON, AND LACKNER, JULIUS E.), Effect of ovarian hormones on human (nonpuerperal) uterus, 379
- , (WITH LACKNER, JULIUS E., AND KROHN, LEON), Etiology and treatment of primary dysmenorrhea, 248
- SPIELMAN, FRANK, Diffuse squamous cell carcinoma of uterus, 159
- T
- TAUSSIG, FRED J., Story of prenatal care, 731
- TEEL, HAROLD M., AND REID, DUNCAN E., Eclampsia and its sequelae, 12
- THOMS, HERBERT, Uses and limitations of roentgen pelvimetry, 150
- THUDIUM, WILLIAM J., (WITH SCHEFFEY, LEWIS C.), Experience in treatment of carcinoma of fundus of uterus, 1006
- TRAUT, HERBERT F., Pyloureteritis in pregnancy, 392
- , AND BUTTERWORTH, J. S., Theca, granulosa, lutein cell tumors of human ovary and similar tumors of mouse's ovary, 987
- TRITSCH, JOHN E., AND BEHM, KARL H., Clinical experience with a new ergot alkaloid, 676
- TRUMP, RUTH A., (WITH FINOLA, GEORGE C., AND GRIMSON, MOZELLE), Bone changes in fetus following administration of dicalcium-phosphate and viosterol to pregnant mother, 955
- U
- URDAN, BENJAMIN E., Three cases of placenta previa following tubal inflation, 142
- W
- WATSON, B. P., Sterilization from point of view of obstetrician and gynecologist, 512
- WATTS, RUTH M., (WITH ADAIR, FRED L.), Study of hormonal content of ovarian cyst fluids, 799
- WERTENBERGER, GRACE E., (WITH COLLETT, MARY E. ET AL.), Effect of estrin upon basal metabolism rate and nervous symptoms of ovariectomized women, 639
- WILLIAMS, PHILIP F., Stillbirth problem, 940
- WILSON, KARL M., Pregnancy complicated by ovarian and parovarian tumors, 977
- WIMPFHEIMER, SEYMOUR, Menstrual fistula (tubo-abdominal), 146
- WOOD, GLENN A., Analysis of 300 consecutive cases of primary cervical repair, 606
- WYCKHOFF, JOHN, Sterilization from standpoint of internist, 520

- LAEMLE, ROBERT M., (WITH BARR, JOSEPH L., AND REIS, RALPH A.), Prolapse of uterus, 827
- LAMB, ARTHUR E., Heart disease in pregnancy, 456
- LONG, SARA, J., (WITH COLLETT, MARY E. ET AL.), Effect of estrin upon basal metabolism rate and nervous symptoms of ovariectomized women, 639
- LUICKART, RALPH, Modification of Kiehlund, Simpson, and Tucker-McLane forceps to simplify their use and improve function and safety, 686
- LUTZ, MARTIN H., Ectopic gestation following Pomeroy sterilization, 497

M

- MACGREGOR, ARTHUR S., Abdominal pregnancy near term, operation and hormonal studies of blood and urine with placenta left in situ, 1030
- MATTHEWS, HARVEY B., Continuous auscultation of fetal heart by means of amplifying stethoscope, 898
- MAYER, MAX D., Status of psychotherapy in gynecologic practice, 47
- MCWILLIAMS, WILLIAM J., Legal considerations for physician, 615
- MILLER, JAMES RAGLAN, Testicular tubular adenoma (Pick), 680
- MILLER, LEON, Diagnosis of extrauterine pregnancy, 109
- MILLER, NORMAN F., AND BROWN, WILLIS, Surgical treatment of complete perineal tears in female, 196
- MINTZ, MAURICE E., Treatment of obstructed fallopian tubes in sterility by diathermy and tubal insufflation, 93
- MURPHY, DOUGLAS P., Etiology of congenital malformations in light of biologic statistics, 890
- MUSA, GEORGE, (WITH HELLMAN, ALFRED M.), Studies on dried blood serum of women, 656
- MUSSEY, ROBERT D., (WITH HUNT, ARTHUR B.), Delivery following stillbirth from dystocia in previous pregnancies, 310

N

- NOVAK, EMIL, Some less generally recognized aspects of gynecologic endocrinology, 237
- , AND ANDERSON, DAVID FYFE, Sarcoma of uterus, 740

P

- PARDEE, HAROLD E. B., Cardiac functional capacity as an aid to prognosis during pregnancy, 557
- PARKER, ELIZABETH, (WITH KOTZ, JACOB), Primary dysmenorrhea—an endocrine problem, 38
- PASTORE, JOHN B., A satisfactory leg support for lithotomy position, 168
- PAYNE, FRANKLIN L., Clinical significance of endometrial hyperplasia, 762
- , (WITH KEENE, FLOYD E.), Treatment of functional uterine hemorrhage, 688
- PHANEUF, LOUIS E., Voluminous hernia of culdesac of Douglas treated by total colectomy, 152
- POSNER, A. CHARLES, Purpura hemorrhagica complicating puerperium, 155

- POTTER, SAMUEL B., Incidence of trichomonas vaginalis infections, 169
- POWER, R. M. H., (WITH GOODALL, J. R.), Modification of Le Fort operation for increasing its scope, 968
- PRATHER, GEORGE C., (WITH CRABTREE, E. GRANVILLE, AND PRIEN, EDWIN L.), End-results of urinary tract infections associated with pregnancy, 405
- PRIEN, EDWIN L., (WITH CRABTREE, E. GRANVILLE, AND PRATHER, GEORGE C.), End-results of urinary tract infections associated with pregnancy, 405

R

- REED, FAITH, W., (WITH COLLETT, MARY E. ET AL.), Effect of estrin upon basal metabolism rate and nervous symptoms of ovariectomized women, 639
- REID, DUNCAN E., (WITH TEEL, HAROLD M.), Eclampsia and its sequelae, 12
- REIS, RALPH A., Intestinal obstruction complicated by pregnancy at term, 1038
- , (WITH BAER, JOSEPH L., AND LAEMLE, ROBERT M.), Prolapse of uterus, 827
- , (WITH DECOSTA, EDWIN J.), Oral administration of paraldehyde for relief of pain during labor, 448
- REYNOLDS, SAMUEL R. M., (WITH LABATE, JOHN S.), Sensory pathways of ovarian plexus, 1
- RICHARDSON, EDWARD H., An efficient composite operation for uterine prolapse and associated pathology, 814
- RIES, EMIL, Episacroiliac lipoma, 490
- ROSEBROOK, L. E., (WITH BRUNER, J. M., AND CUSHMAN, G. W.), Photographic records of cervix uteri, 1027
- ROSEN, JAMES ALAN, (WITH INGRAHAM, HAROLD C.), Obstetric analgesia with acid alurate in rectal ether oil, 672
- ROSS, ROBERT A., Observations pertinent to gonadotropic therapy in gynecology, 780
- ROYSTON, G. D., JENSEN, JULIUS, AND HAUPTMAN, H., Tuberculosis and pregnancy, 284

S

- SAGE, EARL C., Missed abortion—a hematomia mole, 163
- SALMON, UDALL J., Parametrial fixation operation for uterine prolapse, 58
- SCHEFFEY, LEWIS C., AND THUDIUM, WILLIAM J., Experience in treatment of carcinoma of fundus of uterus, 1006
- SCHENCK, SAMUEL B., Correspondence, 181
- SCHILLER, WALTER, Pathology of cervix, 430
- SCHMITZ, HERBERT E., Mortality and complications of 3,129 supracervical hysteromyomectomies, 480
- SEEGERS, WALTER H., Nitrogen balance of a young primipara, 1019
- SERBIN, WILLIAM B., Splenomegaly in pregnancy, 486
- SHELDON, EVERETT A., (WITH ANDERSON, MILFORD X.), Granulosa cell carcinoma of ovary in child of three years and nine months, 119
- SIDDALL, R. S., AND CLINTON, W. R., Lymphangioma of ovary, 306
- SIEGLER, SAMUEL L., Triplet pregnancy with papyraceous fetus, 1023

Carcinoma—Cont'd
 granulosa cell, of ovary in child of three years and nine months (Anderson and Sheldon), 119
 of cervix (Auer), 358 (Abst.)
 during pregnancy (Danforth), 365
 following supravaginal hysterectomy, risk of (Fahndrich), 354 (Abst.)
 methods and results of treatment in, at Memorial Hospital (Healy and Frazell), 593
 ten-year statistical report of (Smythe), 317
 uteri (Henriksen), 352 (Abst.)
 relation of parity to (Tompkins), 353 (Abst.)
 of corpus uteri, relationship of late menstruation to (Crossen and Hobbs), 352 (Abst.)
 of fundus of uterus, experience in treatment of (Scheffey and Thudium), 1006
 of uterus, modern treatment of (Diekinson), 355 (Abst.)
 of vulva, treatment of (Carranza), 357 (Abst.)
 reaction, Klein, (Grögler), 349, (Relmers), 349 (Absts.)
 squamous cell, diffuse, of uterus (Spielman), 159
 Cardiac functional capacity as an aid to prognosis during pregnancy (Pardee), 557
 Central Association of Obstetricians and Gynecologists, items of, 548, 1078
 papers of, 183-321
 presidential address, 183
 Cervical cancer, microscopie diagnosis, afford a prognostic guide in, does, (Wetterdal), 350 (Abst.)
 cesarean section, rupture of scar during labor (Fournier and Estienny), 908 (Abst.)
 epithelium, atypical growth induced in (Overholser and Allen), 351 (Abst.)
 repair, primary (Wood), 606
 stump, sarcoma of (Reckmann), 354 (Abst.)
 Cervicovaginitis, treatment of, in children, with silver picrate suppositories (Kobak and Frankenthal), 292
 Cervix, adenocarcinoma of (Norris), 351 (Abst.)
 cancer of (Ulrich), 352 (Abst.)
 advanced, treated with acetone and x-radiation (MacKenzie), 356 (Abst.)
 after subtotal hysterectomy (Séjournet), 354 (Abst.)
 in young women (Düderlein), 353 (Abst.)
 carcinoma of (Auer), 358 (Abst.)
 during pregnancy (Danforth), 365
 methods and results of treatment in, at Memorial Hospital (Healy and Frazell), 593
 ten-year statistical report of (Smythe), 317
 pathology of (Schiller), 430
 uteri, cancer of (Stout), 353 (Abst.)
 radiotherapy of (MacKenzie), 356 (Abst.)
 carcinoma of (Henriksen), 352 (Abst.)
 relation of parity to (Tompkins), 353 (Abst.)
 photographic records of (Bruner, Rosebrook, and Cushman), 1027
 precancerous and carcinoma lesions of (Henriksen), 349 (Abst.)
 Cesarean section, 901 (Absts.); (Hoffström), 901 (Abst.)
 anesthesia for (Brindeau), 902, (Ginglinger), 903 (Absts.)

Cesarean Section—Cont'd
 as method of therapy to maintain circulation of cord (De Guchteneere et al.), 905 (Abst.)
 at Boston Lying-In Hospital (Smith), 901 (Abst.)
 at William H. Coleman Hospital (Gustafson), 906 (Abst.)
 cervical, rupture of scar during labor (Fournier and Estienny), 908 (Abst.)
 deaths from (Huessy), 907 (Abst.)
 in infected cases (Basden), 906 (Abst.)
 in long axis (Bud), 905 (Abst.)
 in obstetric practice, present position of (Banister), 903 (Abst.)
 in Richmond, Virginia (Hudnall), 902 (Abst.)
 indications for (Crichton), 904 (Abst.)
 unusual (Andrews and Nicholls), 905 (Abst.)
 Latzko (Fleischer and Kushner), 905 (Abst.)
 low, at Charité Obstetrical Clinic (Bue et al.), 902 (Abst.)
 distant consequences of (Trilliat), 908 (Abst.)
 parotitis after (Voron, Broehler and Magnin), 907 (Abst.)
 spontaneous labor after (Andérodias and Péry), 908 (Abst.)
 treatment of placenta previa by (Trilliat), 903 (Abst.)
 lower segment (Riddeil), 905 (Abst.)
 pathologic results of (Lindsay), 907 (Abst.)
 performed under spinal anesthesia, avoidance of complications (Thiessen), 906 (Abst.)
 six on same patient (Pemberton), 906 (Abst.)
 Chemical determination of pregnancy by Visseher-Bowman technique (Drabkin and Goldschmidt), 634
 Cholesterolin, blood, and ovarian function (Barsony), 976 (Abst.)
 Chorionepithelioma, study of 5 patients with (Gough), 267
 Chicago Gynecological Society, item of, 547
 transactions of, 528, 1048
 Circulation of cord, cesarean section as method of therapy to maintain (De Guchteneere et al.), 905 (Abst.)
 Collective review, menstruation and its disorders (Ehrenfest), 530, 699, 1051
 Contraception as a therapeutic measure (Moses), 342 (B. Rev.)
 Colpectomy, total, voluminous hernia of culdesac of Douglas treated by (Phaneuf), 152
 Contraception, medical history of (Hines), 342 (B. Rev.)
 Contractions of nonpregnant human uterus, study of (Robertson), 1047 (Abst.)
 Cord, circulation of, cesarean section as method of therapy to maintain (De Guchteneere et al.), 905 (Abst.)
 Corpus uteri, carcinoma of, relationship of late menstruation to (Crossen and Hobbs), 352 (Abst.)
 Correspondence, 181, 526, 730, 1076
 Culdesac of Douglas, voluminous hernia of, treated by total colpectomy (Phaneuf), 152
 Cyst fluids, ovarian, hormonal content of, study of (Adair and Watts), 799
 Cystocela, Bissell operation for (Grad), 689
 operation, retrograde (Bubis), 225

SUBJECT INDEX*

A

- Abdominal pregnancy near term, operation and hormonal studies of blood and urine with placenta left in situ (MaeGregor), 1030
- Aberrant suprarenal gland tissue in broad ligament (Gough), 1040
- Abortion, criminal, tetanus associated with (Koinaromy), 687
- missed—a hematoma mole (Sage), 163
- Abstracts, carcinoma, 349
- cesarean section, 901
- miscellaneous, 11, 25, 46, 67, 84, 102, 129, 141, 158, 195, 209, 247, 266, 316, 391, 404, 419, 455, 498, 575, 615, 632, 638, 679, 685, 939, 976, 1037, 1047
- Acid alurate in rectal ether oil, obstetric analgesia with (Ingraham and Rosen), 672
- Actinomyces of ovary (Falls), 1033
- Adenocarcinoma of cervix (Norris), 351 (Abst.)
- Adenoma, testicular tubular (Pick) (Miller), 680
- Advisory Board for Medical Specialties, item of, 364
- Alkaloid, ergot, clinical experience with a new (Tritsch and Behni), 676
- Amenorrhea and sterility, treatment of, by radiation (Kaplan), 420
- treatment of undernutrition and secondary (Vogt), 360 (Abst.)
- American Board of Obstetrics and Gynecology, items of, 181, 364, 547, 730, 909, 1078
- Gynecological Society, item of, 181
- number, 731-910, 911, 968, 977
- Analgesia and anesthesia and their bearing upon problem of shortened labor (Bill), 868
- obstetric, atelectasis as a complication of (Cheatham), 166
- with acid alurate in rectal ether oil (Ingraham and Rosen), 672
- Anesthesia and analgesia and their bearing upon problem of shortened labor (Bill), 868
- for cesarean section (Brindeau), 903, (Ginglinger), 903 (Absts.)
- spinal, cesarean section performed under, avoidance of complications in (Thiessen), 906 (Abst.)
- Angiomatosis retinae complicated by pregnancy (Armstrong), 494
- Arbeitsphysiologie der Schwangerschaft (Staehler), 177 (B. Rev.)
- Aschheim-Zondek test for pregnancy, method for ovarian transplantation on rabbits used for (Campbell), 363 (Abst.)
- Atelectasis as a complication of obstetric analgesia (Cheatham), 166
- Auscultation, continuous, of fetal heart by means of amplifying stethoscope (Matthews), 898
- Avitaminosis in coli bacillus infections of pregnancy, rôle of (Courtois et al.), 129 (Abst.)

B

- Baby and growing child (Fischer), 179 (B. Rev.)
- Basal metabolism rate, effect of estrin upon, and nervous symptoms of ovariectomized women (Collett et al.), 639

- Being born (Strain), 178 (B. Rev.)
- Bicornuate uterus, unilateral gonorrheal salpingitis in (James), 1045
- Biologic statistics, congenital malformations in light of, etiology of (Murphy), 890
- Birth control in India (Pillay), 25 (Abst.)
- growth before, rate of (Buchner), 195 (Abst.)
- Bissell operation for cystocele (Grad), 589
- Bleeding, functional puberty, etiology of, and treatment by hormonal therapy (Witherspoon and Collins), 363 (Abst.)
- in late pregnancy (Waters), 455 (Abst.)
- uterine, in preclimacterium, treatment of (Joachimovits), 362 (Abst.)
- Blood and urine, hormonal studies of, abdominal pregnancy near term, operation and, with placenta left in situ (MaeGregor), 1030
- cholesterin and ovarian function (Barsony), 976 (Abst.)
- serum, dried, of women, studies on (Hellman and Musa), 656
- new modification of Friedman test using (Di Gioia), 1037 (Abst.)
- Blutung und Fluor (Runge), 339 (B. Rev.)
- Bone changes in fetus following administration of dicalcium-phosphate and viosterol to pregnant mother (Finola, Trump, and Grinson), 955
- Book reviews, 172, 336
- Books received, 729, 1077
- Born, being (Strain), 178 (B. Rev.)
- Breast, hypertrophy of, massive puberty (Gaines), 130
- British College of Obstetricians and Gynecologists, item of, 1078
- Broad ligament, aberrant suprarenal gland tissue in (Gough), 1040
- Brooklyn Gynecological Society, transactions of, 528, 698, 1048

C

- Cancer, cervical, microscopic diagnosis, does, afford a prognostic guide in (Wetterdal), 350 (Abst.)
- of body of uterus after irradiation for metrorrhagia (Fournier), 355 (Abst.)
- of cervix (Ulrich), 352 (Abst.)
- advanced, treated with acetone and x-radiation (Mackenzie), 356 (Abst.)
- after subtotal hysterectomy (Séjournet), 354 (Abst.)
- in young women (Döderlein), 353 (Abst.)
- uteri (Stout), 353 (Abst.)
- radiotherapy of (Mackenzie), 356 (Abst.)
- of female genitalia, surgical treatment of (Salacz), 357 (Abst.)
- Cancerization of fibroids (Barthélemy), 355 (Abst.)
- Carcinoma, 349 (Absts.)
- cervices, radium treatment of, corporeal recurrence after (Malpas), 356 (Abst.)
- genital, therapy of, relation between histology, prognosis and (Feldwig), 350 (Abst.)

*July, pp. 1-182; August, pp. 183-364; September, pp. 365-548; October, pp. 549-730; November, pp. 731-910; December, pp. 911-1092.

- Gland, interstitial, in human beings (Freiman), 685 (Abst.)
 tissue, aberrant suprarenal, in broad ligament (Gough), 1040
- Gonadotropic stimulation therapy (Zondek), 360 (Abst.)
 therapy in gynecology, observations pertinent to (Ross), 780
- Gonorrhea in female treated by combined heating technic (Bierman and Horowitz), 68
- Gonorrheal salpingitis, unilateral, in bicornuate uterus (James), 1045
- Granulosa cell carcinoma of ovary in child of three years and nine months (Anderson and Sheldon), 119
 tumors, malignancy of (Compton), 85
 theca and lutein, of human ovary and similar tumors of mouse's ovary (Traut and Butterworth), 987
- Gynecologic endocrinology, some less generally recognized aspects of (Novak), 237
 practice, status of psychotherapy in (Mayer), 47
- Gynecologist and obstetrician, sterilization from point of view of (Watson), 512
- Gynecology, 336 (B. Rev.)
 abortion, criminal, tetanus associated with (Komaromy), 687
 missed—a hematoma mole (Sage), 163
 actinomycosis of ovary (Falls), 1033
 adenocarcinoma of cervix (Norris), 351 (Abst.)
 adenoma, testicular tubular (Miller), 680
 amenorrhea and sterility, treatment of, by radiation (Kaplan), 420
 and obstetricians, (Jameson), 336 (B. Rev.)
 department of practical problems in, 322, 688
 cancer of body of uterus after irradiation for metrorrhagia (Fournier), 355 (Abst.)
 of cervix (Ulrich), 352 (Döderlein), 353 (Absts.)
 advanced, treated with acetone and x-radiation (MacKenzie), 356 (Abst.)
 after subtotal hysterectomy (Séjournet), 354 (Abst.)
 uteri (Stout), 353 (Abst.)
 radiotherapy of (MacKenzie), 356 (Abst.)
 of female genitalia, surgical treatment of (Salacz), 357 (Abst.)
 carcinoma granulosa cell, of ovary in child of three years and nine months (Anderson and Sheldon), 119
 of cervix (Auer), 358 (Abst.)
 during pregnancy (Danforth), 365
 methods and results of treatment in, at Memorial Hospital (Healy and Frazell), 593
 ten-year statistical report of (Smythe), 317
 uteri (Henriksen), 352 (Abst.)
 relation of parity to (Tompkins), 353 (Abst.)
 of corpus uteri, relationship of late menstruation to (Crossen and Hobbs), 352 (Abst.)
 of uterus, modern treatment of (Dickinson), 355 (Abst.)
 of vulva, treatment of (Carranza), 357 (Abst.)
 squamous cell, diffuse, of uterus (Spielman), 159
 cervical repair, primary (Wood), 606
- Gynecology—Cont'd
 cervicovaginitis, treatment of, in children with silver pierate suppositories (Kobak and Frankenthal), 292
 chorionepithelioma, study of 5 patients with (Gough), 267
 colpectomy, total, voluminous hernia of culdesae of Douglas treated by (Phaneuf), 152
 cystocele, Bissell operation for (Grad), 589
 discharge, vaginal (Renton), 1047 (Abst.)
 dysmenorrhea, primary—an endocrine problem (Kotz and Parker), 38
 etiology and treatment of (Laekner, Krohn, and Soskin), 248
 endocervicitis, treatment of, a new type of syringe adapted for (Fallon and Douglass), 170
 fibroids, cancerization of (Barthélemy), 355 (Abst.)
 fistula, menstrual (Wimpfheimer), 146
 for nurses (Crossen and Douglas), 339 (B. Rev.)
 gonadotropic therapy in, observations pertinent to (Ross), 780
 gonorrhea in female treated by combined heating technique (Bierman and Horowitz), 68
 hemorrhage, functional uterine, treatment of (Keene and Payne), 688
 hernia, voluminous, of culdesae of Douglas treated by total colpectomy (Phaneuf), 152
 hydatid mole in 55-year-old woman (Feenders), 939 (Abst.)
 hysterectomy, supravaginal, risk of carcinoma of cervix following (Fahndrich), 354 (Abst.)
 hysterotomy for placenta previa in Obstetrical Clinic of Lyon (Voron et al.), 902 (Abst.)
 inflammatory disease, pelvic, uretero-hydronephrosis resulting from (Klempner), 125
 lipoma, episcroliac (Ries), 490
 lymphangioma of ovary (Siddall and Clinton), 306
 mole, hematoma—missed abortion (Sage), 163
 mycoses, vulvovaginal, biologic and clinical import of (Hesseltine), 855
 experimental and clinical therapy of (Hesseltine), 439
 operation, Bissell, for cystocele (Grad), 589
 cystocele, retrograde (Bubis), 225
 for uterine prolapse, an efficient composite, and associated pathology (Richardson), 814
 Le Fort, modification of, for increasing its scope (Goodall and Power), 968
 parametrial fixation, for uterine prolapse (Salmon), 58
 pelvimetry, roentgen, uses and limitations of (Thoms), 150
 prolapse of uterus (Baer, Reis, and Laemle), 827
 uterine, parametrial fixation operation for (Salmon), 58
 purpura hemorrhagica complicating puerperium (Posner), 155
 pyeloureteritis in pregnancy (Traut), 392
 radiotherapy of cancer of cervix uteri (MacKenzie), 356 (Abst.)
 radium treatment of carcinoma cervicis, corporeal recurrence after (Malpas), 356 (Abst.)
 salpingitis, gonorrheal, unilateral, in bicornuate uterus (James), 1045

D

- Delivery following stillbirth from dystocia in previous pregnancies (Hunt and Mussey), 310
- Department of practical problems in obstetrics and gynecology, 322, 688
- Detachment of bladder and urethra, unusual obstetric injury causing, from symphysis pubis and complete epispadias (Hunner), 840
- Diabetes mellitus and pregnancy (Kraus), 129 (Abst.)
- Diathermy and tubal insufflation, treatment of obstructed fallopian tubes in sterility by (Mintz), 93
- Dicalcium-phosphate and viosterol, bone changes in fetus following administration of, to pregnant mother (Finola, Trump, and Grimson), 955
- Dictionnaire, medical (Stedman), 348 (B. Rev.)
- Die Erbsenkrankheiten, Eklampischen, 76 (B. Rev.)
- Die Gynaekologischen Operationen (Marthus), 336 (B. Rev.)
- Die Kuenstliche Scheidenbildung aus dem Mastdarm (Schubert), 337 (B. Rev.)
- Diet, balanced (Clendening), 348 (B. Rev.)
- Discharge, vaginal (Renton), 1047 (Abst.)
- Dried blood serum of women, studies on (Hellman and Musa), 656
- Dysmenorrhea, endocrinal origin of primary, and its hormonal treatment (Witherspoon), 361 (Abst.)
- primary—an endocrine problem (Kotz and Parker), 38
- etiology and treatment of (Lackner, Krolin, and Soskin), 248
- Dystocia, delivery following stillbirth from, in previous pregnancies (Hunt and Mussey), 310

E

- Eclampsia and its sequelae (Teel and Reid), 12
- prevention of (De Snoo), 911
- Ectopic gestation following Pomeroy sterilization (Lutz), 497
- pregnancy, study of 100 consecutive cases of (Grier), 103
- Editorial, 1049
- Eggs of mammals (Pincus), 346 (B. Rev.)
- Emmenin, use of (Goldberg and Lisser), 360 (Abst.)
- Emotional problems, single woman and her (Hutton), 340 (B. Rev.)
- Endocervicitis, treatment of, a new type of syringe adapted for (Fallon and Douglass), 170
- Endocrine diagnosis, status of biometry in (Berkow), 114
- problem—primary dysmenorrhea (Kotz and Parker), 38
- Endocrinologic study, true hermaphroditism in man with an (Huggins, Cohen, and Harden), 136
- Endocrinology, gynecologic, some less generally recognized aspects of (Novak), 237
- in modern practice (Wolf), 180 (B. Rev.)
- Endometrial hyperplasia, clinical significance of (Payne), 762
- Endometriosis of uterine adnexa (Barsony), 419 (Abst.)
- Episacroiliac lipoma (Ries), 490

- Epispadias, complete, unusual obstetric injury causing detachment of bladder and urethra from symphysis pubis and (Hunner), 840
- Ergebnisse der Medizinischen Strahlenforschung (Holfelder et al.), 338 (B. Rev.)
- Ergot alkaloid, new, clinical experience with (Tritsch and Behm), 676
- Erythroblastosis fetalis as a cause of infantile mortality (Javert), 1042
- Estrin, effect of, upon basal metabolism rate and nervous symptoms of ovariectomized women (Collett et al.), 639
- Estrogenic principle, effects of large doses of, evaluation of constitutional (Mazer et al.), 362 (Abst.)
- Ether oil, rectal, obstetric analgesia with acid alurate in (Ingraham and Rosen), 672
- Eugenic sterilization laws in Europe (Kopp), 499
- Eugenics and sterilization (Kennedy), 519
- Extrauterine pregnancy, diagnosis of (Miller), 109

F

- Fallopian tubes in sterility, treatment of obstructed, by diathermy and tubal insufflation (Mintz), 93
- Fear (Hamilton), 183
- Fetus, bone changes in, following administration of dicalcium-phosphate and viosterol to pregnant mothers (Finola, Trump, and Grimson), 955
- Fetal heart, auscultation of, continuous, by means of amplifying stethoscope (Matthews), 898
- Fetus, human, diagnosis of sex of, in utero (Blakely), 322
- papyraceous, triplet pregnancy with (Sieglar), 1023
- Fibroid, cancerization of (Barthélemy), 355 (Abst.)
- of uterus, pregnancy complicated, triple diagnostic error in case of (Lucchetti), 1039 (Abst.)
- Fille ou Garçon (Regnault), 348 (B. Rev.)
- First All-India Obstetric and Gynecological Congress, Madras, 178 (B. Rev.)
- Fistula, menstrual (Wimpfheimer), 146
- Food, fitness and figure (Buckstein), 347 (B. Rev.)
- Forceps, Keilland, Simpson, and Tucker-McLane, modification of, to simplify their use and improve function and safety (Luikart), 686
- Friedman test, studies of difficulties encountered in (Di Gioia), 1037 (Abst.)
- Functional uterine hemorrhage, treatment of (Keene and Payne), 688

G

- Genital carcinoma, therapy of, relation between histology, prognosis and (Feldwig), 350 (Abst.)
- Genitalia, female, cancer of, surgical treatment of (Salacz), 357 (Abst.)
- malignant conditions of, intraspinal injections of alcohol for pain associated with (Greenhill and Schmitz), 358 (Abst.)
- mumps and (Bosch), 575 (Abst.)
- Gestation, ectopic, following Pomeroy sterilization (Lutz), 497

In Table I is shown the time elapsed from the onset of symptoms to the day of operation. Two-thirds of these women went two weeks and the other third from three to ten weeks. The earlier a diagnosis can be made the better the prognosis for the patient. But on the other

TABLE I. TIME FROM ONSET OF SYMPTOMS TO DAY OF OPERATION IN 90 RECORDED CASES

Same day	16.6%	} 66.5%
First week	31.1%	
Second week	18.8%	
Third week	12.2%	
Fourth week	5.5%	
Fifth week	3.3%	
Sixth week	5.5%	
Seventh week	3.3%	
Eighth week	2.2%	
Tenth week	1.1%	
		99.6%

hand these figures show that the patient's condition may not be critical for quite some time. Usually sufficient time may be taken for adequate examination. However, if an ectopic pregnancy is suspected, the patient is much safer in a hospital where repeated blood counts can be taken and constant observation is possible. A blood grouping should be taken for transfusion in case of an emergency. Laparotomy and excision of the pregnant tube should be done as soon as a diagnosis is made. It is better to operate too often for ectopic pregnancy than not often enough. Posterior colpotomy was carried out in a few of the first fifty cases and in none of the latter. A curettage prior to laparotomy was done only fourteen times. Usually this was because a diagnosis of incomplete abortion had been made. As a diagnostic procedure it should be done infrequently. Our experience has shown that following curettage or colpotomy the morbidity is greatly increased. The time spent in the hospital usually was not long before diagnosis was established. In this series, 48 per cent were operated upon on the day of admission and only 16 per cent after the third day. Other pathologic conditions were often encountered. The incidence of salpingitis was lower than reported in most other studies, being only 17 per cent. Ovarian and parovarian cysts were noted in 18 per cent, chronic appendicitis in 4 per cent, and uterine fibroma in 4 per cent.

As a rule one should not attempt to do anything more than a removal of the affected tube. Our usual procedure was the same as formerly reported. The abdomen was quickly opened. The presence of free blood at once confirmed the diagnosis. The offending tube was located as quickly as possible. If so much blood was present that the pelvic structures were obscured, the pregnant tube was rapidly located by the palpating fingers. It was brought into view and a clamp placed on the uterine end and another just outside the fimbriated end. If the condi-

Gynecology—Cont'd

- sarcoma of cervical stump (Reckmann), 354 (Abst.)
 of uterus (Novak and Anderson), 740
 sterility and amenorrhea, treatment of, by radiation (Kaplan), 420
 study of, an aid in (Krigbaum), 1046
 surgical treatment of complete perineal tears in female (Miller and Brown), 196
 toxemias, hypertension, and nephritis of pregnancy (Douglas), 565
 trichomonas vaginalis infections, incidence of (Potter), 169
 tumors, granulosa cell, malignancy of (Compton), 85
 malignant, effect of pregnancy on (Smith), 616
 ovarian and parovarian, pregnancy complicated by (Wilson), 977
 theca, granulosa and luteal cell, of human ovary and similar tumors of mouse's ovary (Traut and Butterworth), 987
 urterohydronephrosis resulting from pelvic inflammatory disease (Klemmner), 125

H

- Heart disease in pregnancy (Lamb), 456
 management of (Jensen), 904 (Abst.)
 fetal, auscultation of, continuous, by means of amplifying stethoscope (Matthews), 898
 Heating technique, combined, gonorrhea in female treated by (Bierman and Horowitz), 68
 Hematoma mole—missed abortion (Sage), 163
 Hemorrhage, functional uterine, treatment of (Keene and Payne), 688
 postclimacteric, and their relation to malignant neoplasms (Wittenbourg and Zlatmann), 352 (Abst.)
 Hermaphroditism, true, in man with an endocrinologic study (Huggins, Cohen, and Harden), 136
 Hernia, voluminous, of oviducts of Douglas treated by total colectomy (Phaneuf), 152
 Hormonal content of ovarian cyst fluids, study of (Adair and Watts), 799
 studies of blood and urine, abdominal pregnancy near term, operation and, with placenta left in situ (MacGregor), 1030
 therapy for menstrual disturbances (Westman), 358 (Abst.)
 treatment by, etiology of functional puberty bleeding and (Witherspoon and Collins), 363 (Abst.)
 treatment of dysmenorrhea, primary, endocrinal origin of (Witherspoon), 361 (Abst.)
 Hormones, estrogenic and luteal, treatment of amenorrhea by (Vogt), 360 (Abst.)
 ovarian and pituitary (Fairlie), 359 (Abst.)
 effect of, on human (nonpuerperal) uterus (Krohn, Lackner and Soskin), 379
 sex, treatment with female (Neumann), 358 (Abst.)
 Hydatid mole in 55-year-old woman (Feenders), 939 (Abst.)
 Hydramnios during pregnancy, percutaneous puncture for (Mayer), 498 (Abst.)
 Hygiene, woman's, facts and frauds in (Palmer and Greenberg), 340 (B. Rev.)

- Hyperplasia, endometrial, clinical significance of (Payne), 762
 Hypertension, menopausal (Schaefer), 362 (Abst.)
 nephritis, and toxemias of pregnancy (Douglas), 565
 Hypertrophy, puberty, massive, of breasts (Gaines), 130 (Abst.)
 Hypophysis, implantation of, treatment of amenorrhea by (Vogt), 360 (Abst.)
 Hysterectomy, subtotal, cancer of cervix after (Séjournet), 354 (Abst.)
 supravaginal, risk of carcinoma of cervix following (Fahndrich), 354 (Abst.)
 Hysteromyomectomies, supraeervical, mortality and complications of 3,129 (Schmitz), 480
 Hysterosalpingography (Lundquist and Runström), 391 (Abst.)
 Hysterotomy for placenta previa in Obstetrical Clinic of Lyon (Voron et al.), 902 (Abst.)

I

- Incontinence of urine in female (Kennedy), 576
 Infant mortality, factors responsible for failure further to reduce, 1049 (Edit.)
 Infantile mortality, erythroblastosis fetalis as cause of (Javert), 1042
 Infections, trichomonas vaginalis, incidence of (Potter), 169
 urinary tract, end-results of, associated with pregnancy (Crabtree, Prather and Prien), 405
 Inflation, tubal, placenta previa following (Urdan), 142
 Injury, obstetric, unusual, causing detachment of bladder and urethra from symphysis pubis and complete epispadias (Hunner), 840
 Insufflation, tubal, treatment of obstructed fallopian tubes in sterility by diathermy and (Mintz), 93
 Internist, sterilization from standpoint of (Wyckhoff), 520
 International Congress of Obstetrics and Gynecology, item of, 548
 Interstitial glands in human beings (Freiman), 685 (Abst.)
 Intestinal obstruction complicated by pregnancy at term (Reis), 1038
 Intraspinal injections of alcohol for pain associated with malignant conditions of female genitalia (Greenhill and Schmitz), 358 (Abst.)
 Intravenous use of gum acacia glueose infusions, severe and fatal reactions following (Studdiford), 615 (Abst.)
 Irradiation for metrorrhagia, cancer of body of uterus after (Fournier), 355 (Abst.)
 sterilization by (Kaplan), 507
 Items, Advisory Board for Medical Specialties, 364
 American Board of Obstetrics and Gynecology, 181, 364, 547, 730, 909, 1078
 Gynecological Society, 181
 British College of Obstetricians and Gynecologists, 1078
 Central Association of Obstetricians and Gynecologists, 548, 1078
 Chicago Gynecological Society, 547
 International Congress of Obstetrics and Gynecology, 548
 Mississippi Valley Medical Society, 909
 Pittsburgh Obstetrical and Gynecological Society, 1077

K

- Kiefland forceps, modification of, to simplify their use and improve function and safety (Lulkart), 686
 Konservative Therapie der Frauenkrankheiten (Kahr), 339 (B. Rev.)

L

- Labor, pain during, relief of, oral administration of paraldehyde for (DeCosta and Reis), 448
 problem of shortened, analgesia and anesthesia and their bearing upon (Bill), 868
 rupture of cervical cesarean section scar during labor (Fournier and Estienny), 908 (Abst.)
 spontaneous, after low cesarean section (Andérodias and Péry), 908 (Abst.)
 Latzko cesarean section (Fleischer and Kushner), 905 (Abst.)
 Le Fort operation, modification of, for increasing its scope (Goodall and Power), 968
 Leg support for lithotomy position, satisfactory (Pastore), 168
 Legal consideration for physician, relating to sterilization (McWilliams), 516
 Les Problèmes D'Oncologie, 347 (B. Rev.)
 Lindau's disease complicated by pregnancy (Armstrong), 494
 Lipoma, episacroiliac (Ries), 490
 Lithotomy position, leg support for, satisfactory (Pastore), 168
 Lutein cell tumors, theca and granulosa, of human ovary and similar tumors of mouse's ovary (Traut and Butterworth), 987
 Lymphangioma of ovary (Siddall and Clinton), 306
 Lymphogranuloma inguinale of female urethra (Gray), 247 (Abst.)
 Lymphopathia venerea, Frei test in, specificity of (Bacon), 158 (Abst.)

M

- Malformations, congenital, etiology of, in light of biologic statistics (Murphy), 890
 Married, engaged and single (Chideckel), 343 (B. Rev.)
 woman (Groves and Ross), 341 (B. Rev.)
 Maternal morbidity (Grier), 298
 Maternity services (Browne), 67 (Abst.)
 Medical classics (Kelly), 343 (B. Rev.)
 dictionary (Stedman), 348 (B. Rev.)
 history of contraception (Hines), 342 (B. Rev.)
 Medicine and mankind, 344 (B. Rev.)
 Menopausal hypertension (Schaefer), 362 (Abst.)
 Menstrual disturbances, hormonal therapy for (Westman), 358 (Abst.)
 fistula (Wimpfheimer), 146
 Menstruation and its disorders (Ehrenfest), 530, 699, 1051 (Collect. Rev.)
 relationship of late, to carcinoma of corpus uteri (Crossen and Hobbs), 352 (Abst.)
 Metabolism rate, basal, effect of estrin upon, and nervous symptoms of ovariectomized women (Collett et al.), 639
 Metrorrhagia, irradiation for, cancer of body of uterus after (Fournier), 355 (Abst.)
 Midwifery services (Moyes), 141 (Abst.)

- Migraine and ovarian deficiency (Glass), 361 (Abst.)
 Mississippi Valley Medical Society, item of, 909
 Mole, hematoma—missed abortion (Sage), 163
 Morbidity, maternal (Grier), 298
 Mortality and complications of, 3,129
 supracervical hysteromyomectomies (Schmitz), 480
 infant, factors responsible for failure further to reduce, 1049 (Edit.)
 infantile, erythroblastosis fetalis as cause of (Javert), 1042
 Mumps and female genitalia (Bosch), 575 (Abst.)
 Myeoses, vulvovaginal, biologic and clinical import (Hesseltine), 855
 experimental and clinical therapy of (Hesseltine), 439

N

- Nel Trentesimo di Fondazione, Della R. Clinica Ostetrico-Ginecologica "Luigi Mangiagalli" di Milano, 177 (B. Rev.)
 Neoplasms, malignant, postclimacteric hemorrhages and their relation to (Wittenbourg and Zlatmann), 352 (Abst.)
 Nephritis, hypertension, and toxemias of pregnancy (Douglas), 565
 Nervous disease, preface to (Cobb), 347 (B. Rev.)
 symptoms, effect of estrin upon basal metabolism rate and, of ovariectomized women (Collett et al.), 639
 Nevus telangiectaticus and pregnancy (Wirth), 11 (Abst.)
 Newborn, surgery in (Harrar), 661
 New York Academy of Medicine, section on obstetrics and gynecology, transactions of, 529
 Obstetrical Society, transactions of, 527, 698
 Nitrogen balance of young primipara (Seegers), 1019
 Nurses, gynecology for (Crossen and Crossen), 339 (B. Rev.)
 Nursing, pediatric (Zahorsky), 179 (B. Rev.)

O

- Obstetric analgesia, atelactasis as a complication of (Cheatham), 166
 with acid alurate in rectal ether oil (Ingraham and Rosen), 672
 difficulties, management of (Titus), 173 (B. Rev.)
 injury, unusual, causing detachment of bladder and urethra from symphysis pubis and complete epispadias (Hunner), 840
 practice, cesarean section in, present position of (Banister), 903 (Abst.)
 Obstetrical Society of Philadelphia, transactions of, 528, 1048
 Obstetrician and gynecologist, sterilization from point of view of (Watson), 512
 Obstetrics, 172 (B. Rev.)
 and gynecology (Jameson), 336 (B. Rev.)
 department of practical problems in, 322, 688
 cesarean section, 901 (Abst.); (Hoffström), 901 (Abst.)
 anesthesia for (Brindeau), 903, (Ginglinger), 903 (Absts.)
 as method of therapy to maintain circulation of cord (De Guchteneere et al.), 905 (Abst.)
 at Boston Lying-In Hospital (Smith), 901 (Abst.)

- Obstetrics, cesarean section—Cont'd
 at William H. Coleman Hospital (Gustafson), 906 (Abst.)
 cervical, rupture of scar during labor after (Fournier and Estienny), 908 (Abst.)
 deaths from (Huessey), 907 (Abst.)
 in infected cases (Basden), 906 (Abst.)
 in long axis (Bud), 905 (Abst.)
 in obstetric practice, present position of (Banister), 903 (Abst.)
 in Richmond, Virginia (Hudnall), 902 (Abst.)
 indications for (Crichton), 904 (Abst.)
 unusual (Andrews and Nicholls), 905 (Abst.)
 Latzko (Fleischer and Kushner), 905 (Abst.)
 low at Charité Obstetrical Clinic (Bue et al.), 902 (Abst.)
 distant consequences of (Trillat), 908 (Abst.)
 parotitis after (Voron et al.), 907 (Abst.)
 treatment of placenta previa by (Trillat), 903 (Abst.)
 lower segment (Riddell), 905 (Abst.)
 pathologic results of (Lindsay), 907 (Abst.)
 performed under spinal anesthesia, avoidance of complications in (Thiessen), 906 (Abst.)
 six on same patient (Pemberton), 906 (Abst.)
 delivery following stillbirth from dystocia in previous pregnancies (Hunt and Mussey), 310
 eclampsia and its sequelae (Teel and Reid), 12
 prevention of (De Snoo), 911
 gestation, ectopic following Pomeroy sterilization (Lutz), 497
 labor, pain during, relief of, oral administration of paraldehyde for (DeCosta and Reis), 448
 shortened, analgesia and anesthesia and their bearing upon problem of (Bill), 868
 placenta previa following tubal inflation (Urdu), 142
 hysterotomy for, in Obstetrical Clinic of Lyon (Voron et al.), 902 (Abst.)
 treatment of, by low cesarean section (Trillat), 903 (Abst.)
 practical, manual of (Brown), 175 (B. Rev.)
 pregnancy, abdominal, near term, operation and hormonal studies of blood and urine with placenta left in situ (MacGregor), 1030
 and tuberculosis (Royston, Jensen, and Hauptman), 284
 carcinoma of cervix during (Danforth), 365
 complicated by ovarian and parovarian tumors (Wilson), 977
 complicating intestinal obstruction (Reis), 1038
 ectopic, study of 100 consecutive cases of (Grier), 103
 effect of, on malignant tumors (Smith), 616
 extrauterine, diagnosis of (Miller), 109
 heart disease in (Lamb), 456
 hypertension, nephritis, and toxemias of (Douglas), 565
 late, toxemias of, vascular factor in (Eastman), 549
 mechanism of prolongation of, in rabbit (Koff and Davis), 26
 ovarian (Kanter), 1035
- Obstetrics, pregnancy—Cont'd
 prognosis during, cardiac functional capacity as an aid to (Pardee), 557
 pyeloureteritis in (Traut), 392
 splenomegaly in (Serbin), 486
 surgical complications of (Cosgrove), 469
 triplet, with papyraceous fetus (Siegle), 1023
 twin, analysis of 521 cases of (Guttmaacher), 76
 textbook of (Schumann), 172 (B. Rev.)
 Williams (Stander), 173 (B. Rev.)
 obstruction, intestinal, complicated by pregnancy at term (Reis), 1038
 Oil, rectal ether, obstetric analgesia with acid alurate in (Ingraham and Rosen), 672
 Operation, Bissell, for cystocele (Grad), 589
 cystocele, retrograde (Bubis), 225
 for uterine prolapse, an efficient composite, and associated pathology (Richardson), 814
 Le Fort, modification of, for increasing its scope (Goodall and Power), 968
 parametrial fixation, for uterine prolapse (Salmon), 58
 Operative methods of sterilization in female (Bishop), 505
 Oral thrush and vulvovaginitis, cultural and morphologic studies of erythrocytes and monilia isolated from (Hopkins and Hesselstine), 209 (Abst.)
 Organotherapy, 358 (Absts.)
 Ova, presumable human, six normal and complete (Brewer and Fitzgerald), 210
 Ovarian and parovarian tumors, pregnancy complicated by (Wilson), 977
 and pituitary hormones (Fairlie), 359 (Abst.)
 cyst fluids, hormonal content of, study of (Adair and Watts), 799
 deficiency, migraine and (Glass), 361 (Abst.)
 function, blood cholesterol and (Barsony), 976 (Abst.)
 grafts (Massabuan et al.), 141 (Abst.)
 hormones, effect of, on human (non-puerperal) uterus (Krohn, Laekner and Soskin), 379
 injections of, prolonged, combined with chronic trauma (Overholser and Allen), 351 (Abst.)
 plexus, sensory pathways of (Labate and Reynolds), 1
 pregnancy (Kanter), 1035
 transplantation on rabbits used for Aschheim-Zondek test for pregnancy (Campbell), 363 (Abst.)
 Ovarietomized women, effect of estrin upon basal metabolism rate and nervous symptoms of (Collett et al.), 639
 Ovary, actinomyces of (Falls), 1033
 and tube, unilateral failure of development of, in light of biologic and anatomic knowledge (Lartschneider), 46 (Abst.)
 granulosa cell carcinoma of, in child of three years and nine months (Anderson and Sheldon), 119
 human, theca, granulosa, lutein cell tumors of, and similar tumors of mouse's ovary (Traut and Butterworth), 987
 lymphangioma of (Siddall and Clinton), 306
 Ovary, death of, pregnancy test in relation to (Bishop), 363 (Abst.)
 single and double, twinning, differences in (Guttmaacher), 76

P

- Pain during labor, relief of, oral administration of paraldehyde for, (DeCosta and Reiss), 448
- Papyraceous fetus, triplet pregnancy with (Sieglar), 1023
- Paraldehyde for relief of pain during labor, oral administration of, (DeCosta and Reiss), 448
- Parametrial fixation operation for uterine prolapse (Salmon), 58
- Parotitis after low cesarean section (Voron, et al.), 907 (Abst.)
- Parovarian and ovarian tumors, pregnancy complicated by (Wilson), 977
- Parturition, an evolutionary factor in (Gillies), 102 (Abst.)
- Pastor, physician and patient (Jacoby), 344 (B. Rev.)
- Patient and the weather (Peterson), 347 (B. Rev.)
- physician, and pastor (Jacoby), 344 (B. Rev.)
- Pediatric nursing (Zahorsky), 179 (B. Rev.)
- Pelvic inflammatory disease, ureterohydronephrosis resulting from (Klempner), 125
- Pelvimetry, roentgen, uses and limitations of (Thoms), 150
- Perineal tears, complete, in female, surgical treatment of (Miller and Brown), 196
- Perineum, restoration of, immediate, suture of sphincter with horse-hair in (Mahon), 633 (Abst.)
- Photographic records of cervix uteri (Bruner, Rosebrook, and Cushman), 1027
- Physician, 343 (B. Rev.)
- legal considerations, for, relating to sterilization (McWilliams), 516
- pastor and patient (Jacoby), 344 (B. Rev.)
- true (Johnson), 343 (B. Rev.)
- Physiology and pharmacology of pituitary body (Van Dyke), 179 (B. Rev.)
- Pineal extract, organotherapeutic researches on (Hofstätter), 361 (Abst.)
- Pittsburgh Obstetrical and Gynecological Society, item of, 1077
- Pituitary body, physiology and pharmacology of (Van Dyke), 179 (B. Rev.)
- hormones, ovarian and (Fairlie), 359 (Abst.)
- Placenta, premature separation of normally implanted, conservative treatment of (Irving), 881
- previa following tubal inflation (Urdan), 142
- hysterotomy for, in Obstetrical Clinic of Lyon (Voron et al.), 902 (Abst.)
- treatment of, by low cesarean section (Trilliat), 903 (Abst.)
- Placental insertion in mechanism of rupture of uterus (Orrill), 908 (Abst.)
- Plexus, ovarian, sensory pathways of (Labate and Reynolds), 1
- Polyps, bleeding, of septum (Banssillon and Mounier-Kuh), 25 (Abst.)
- Pomeroy sterilization, ectopic gestation following (Lutz), 497
- Precocious motherhood (Olsen), 316 (Abst.)
- Pregnancy, abdominal, near term, operation and hormonal studies of blood and urine with placenta left in situ (MacGregor), 1030
- and nevus telangiectaticus (Wirth), 11 (Abst.)
- Pregnancy—Cont'd
- and tuberculous (Royston, Jensen, and Hauptman), 284
- bleeding in late (Waters), 455 (Abst.)
- carcinoma of cervix during (Danforth), 365
- chemical determination of, by Visseher-Bowman technique (Drabkin and Goldschmidt), 634
- coli bacillus infections of, rôle of avitaminosis in (Courtois, et al.), 129 (Abst.)
- complicated by fibroid of uterus, triple diagnostic error in case of (Luechetti), 1039 (Abst.)
- ovarian and parovarian tumors (Wilson), 977
- complicating angiomas retinæ (Armstrong), 494
- intestinal obstruction (Reis), 1038
- diabetes mellitus and (Kraus), 129 (Abst.)
- ectopic, study of 100 consecutive cases of (Grier), 103
- effect of, on malignant tumors (Smith), 616
- epistaxis during (Banssillon and Mounier-Kuh), 25 (Abst.)
- extrauterine, diagnosis of (Miller), 109
- heart disease in (Lamb), 456
- management of (Jensen), 904 (Abst.)
- influence of, upon development of teratocarcinoma in white mice, experimental research upon (Cini), 316 (Abst.)
- late, toxemias of, vascular factor in (Eastman), 549
- mechanism of prolongation of, in rabbit (Koff and Davis), 26
- ovarian (Kanter), 1035
- prognosis during, cardiac functional capacity as an aid to (Pardee), 557
- puncture for hydramnios during, percutaneous (Mayer), 498 (Abst.)
- pyeloureteritis in (Traut), 392
- rupture of symphysis during (Hirsch), 404 (Abst.)
- splenomegaly in (Serbin), 486
- surgical complications of, (Cosgrove), 469
- test in relation to death of ovum (Bishop), 363 (Abst.)
- Visseher-Bowman, experiences with (Sehenek and Tran), 526 (Correspondence)
- toxemias of (Mellroy), 175 (B. Rev.)
- hypertension and nephritis (Douglas), 565
- triple, roentgen diagnosis of (Ballard), 526 (Correspondence)
- triplet with papyraceous fetus (Sieglar), 1023
- twin, analysis of 521 cases of (Guttmaehrer), 76
- urinary tract infections associated with (Crabtree, Prather, and Prien), 405
- Pregnant mother, administration of dicaleum-phosphate and viosterol to, bone changes in fetus following (Finola, Trump and Grimson), 955
- Premature separation of normally implanted placenta, conservative treatment of (Irving), 881
- Prenatal care, story of (Taussig), 731
- Presomite human ova, six normal and complete (Brewer and Fitzgerald), 210
- Primipara, nitrogen balance of a young (Seegers), 1019
- Prolapse of uterus (Baer, Reiss, and Laemie), 827
- uterine, operation for, an efficient composite, and associated pathology (Richardson), 814

Prolapse, uterine—Cont'd
parametrial fixation operation for (Salmon), 58
Prostitution (Kemp), 339 (B. Rev.)
Psychology of sex (Ellis), 340 (B. Rev.)
Psychotherapy, status of, in gynecologic practice (Mayer), 47
Puberty bleeding, functional, etiology of, and treatment of hormonal therapy (Witherspoon and Collins), 363 (Abst.)
hypertrophy, massive, of breasts (Gaines), 130
Puerperal tetanus, posthysterectomy and (Pulvertaft), 679 (Abst.)
Puerperium, purpura hemorrhagica complicating (Posner), 155
Pyelitis of defloration (Lepontre), 266 (Abst.)
Pyeloureteritis in pregnancy (Traut), 392

R

Radiation in treatment of amenorrhea and sterility (Kaplan), 420
Radiothérapie Gynécologique (Mathey-Cornat), 338 (B. Rev.)
Radlotherapy of cancer of cervix uteri (Mackenzie), 356 (Abst.)
Radium treatment of carcinoma cervicis, corporeal recurrence after (Malpas), 356 (Abst.)
Rectal ether oil, obstetric analgesia with acid alurate in (Ingraham and Rosen), 672
Repair, cervical, primary (Wood), 606
Restoration of perineum, immediate, suture of sphincter with horsehair in (Mahon), 633 (Abst.)
Résultats des Greffes Ovariennes (Mocquet and Cotte), 337 (B. Rev.)
Review of new books, 172, 336
Roentgen diagnosis of triple pregnancy (Ballard), 526 (Correspondence)
pelvimetry, uses and limitations of (Thoms), 150
Rupture of scar during labor following cervical cesarean section (Fournier and Estienny), 908 (Abst.)
of uterus, placental insertion in mechanism of (Orrul), 908 (Abst.)

S

Salpingitis, gonorrheal, unilateral, in bicornuate uterus (James), 1045
Sarcoma of cervical stump (Reckmann), 354 (Abst.)
of uterus (Novak and Anderson), 740
Schiller test (Hendriksen), 349 (Abst.)
Sensory pathways of ovarian plexus (Labate and Reynolds), 1
Separation, premature, of normally implanted placenta, conservative treatment of (Irving), 881
Serum, blood, dried, of women, studies on (Hellman and Musa), 656
Sex, diagnosis of, of human fetus in utero (Blakely), 322
hormones, female, treatment with (Neumann), 358 (Abst.)
problems, 340 (B. Rev.)
psychology of (Ellis), 340 (B. Rev.)
Silver pierate suppositories, treatment of cervicovaginitis in children with (Kobak and Frankenthal), 292
Simpson forceps, modification of, to simplify their use and improve function and safety (Luikart), 686

Single, engaged and married (Chideckel), 343 (B. Rev.)
Society transactions, Brooklyn Gynecological Society, 528, 698, 1048
Chicago Gynecological Society, 528, 1048
New York Academy of Medicine, section on obstetrics and gynecology, 529
Obstetrical Society, 527, 698
Obstetrical Society of Philadelphia, 528, 1048
Washington Gynecological Society, 529
Sphincter, suture of, with horsehair in immediate restoration of perineum (Mahon), 633 (Abst.)
Spinal anesthesia, cesarean section performed under, avoidance of complications in (Thiessen), 906 (Abst.)
Splénomegaly in pregnancy (Serbin), 486
Squamous cell carcinoma, diffuse, of uterus (Spielman), 159
Sterility and amenorrhea, treatment of, by radiation (Kaplan), 420
fallopian tubes in, treatment of, obstructed, by diathermy and tubal insufflation (Mintz), 93
study of, an aid in (Krigbaum), 1046
Sterilization and eugenics (Kennedy), 519
by irradiation (Kaplan), 507
from point of view of obstetrician and gynecologist (Watson), 512
from standpoint of internist (Wyckhoff), 520
in female, operative methods of (Bishop), 505
laws, eugenics, in Europe (Kopp), 499
legal considerations for physician (McWilliams), 516
Pomeroy, ectopic gestation following (Lutz), 497
symposium on, 499-525
Stethoscope, amplifying, continuous auscultation of fetal heart by means of (Matthews), 898
Stillbirth, delivery following, from dystocia in previous pregnancies (Hunt and Mussey), 310
problem (Williams), 940
Suppositories, silver pierate, treatment of cervicovaginitis in children with (Kobak and Frankenthal), 292
Supracervical hysteromyomectomies, mortality and complications of 3,129 (Schmitz), 480
Suprarenal gland tissue, aberrant, in broad ligament (Gough), 1040
Supravaginal hysterectomy, risk of carcinoma of cervix following (Fahndrich), 354 (Abst.)
Surgery in newborn (Harrar), 661
postgraduate, 345 (B. Rev.)
Surgical complications of pregnancy (Cosgrove), 469
treatment of complete perineal tears in female (Miller and Brown), 196
Suture of sphincter with horsehair in immediate restoration of perineum (Mahon), 633 (Abst.)
Symphysis pubis, detachment of bladder and urethra from, unusual obstetric injury causing, and complete epispadias (Hunner), 840
rupture of, spontaneous, during pregnancy (Hirsch), 404 (Abst.)
Syphilis and its treatment (Hinton), 344 (B. Rev.)
Syringe adapted for treatment of endocervicitis, a new type of (Fallon and Douglass), 170

T

- Tear, perineal, complete, in female, surgical treatment of (Miller and Brown), 196
- Test, Friedman, studies of difficulties encountered in (Di Gioia), 1037 (Abst.)
- pregnancy, in relation to death of ovum (Bishop), 363 (Abst.)
- Testicular tubular adenoma (Piek) (Miller), 680
- Tetanus associated with criminal abortion (Komaromy), 687
- puerperal, posthysterectomy and (Pulvertaft), 679 (Abst.)
- Theca cell, granulosa, lutein cell tumors of human ovary and similar tumors of mouse's ovary (Traut and Butterworth), 987
- Therapeutica das Syndromes Gravidopuerperae (de Camargo), 176 (B. Rev.)
- Tissue, aberrant suprarenal gland, in broad ligament (Gough), 1040
- Toxemias of late pregnancy, vascular factor in (Eastman), 549
- of pregnancy (McIlroy), 175 (B. Rev.)
- hypertension and nephritis (Douglas), 565
- Trichomonas vaginalis infections, incidence of (Potter), 169
- Triplet pregnancy with papyraceous fetus (Sieglar), 1023
- Tubal inflation, placenta previa following (Urdan), 142
- insufflation, treatment of obstructed fallopian tubes in sterility by diathermy and (Mintz), 93
- Tuberculosis and pregnancy (Royston, Jensen, and Hauptman), 284
- Tubular adenoma (Piek), testicular (Miller), 680
- Tucker-McLane forceps, modification of, to simplify their use and improve function and safety (Luikart), 686
- Tumors, granulosa cell, malignancy of (Compton), 85
- theca and lutein cell, of human ovary and similar tumors of mouse's ovary (Traut and Butterworth), 987
- lutein cell, theca and granulosa, of human ovary and similar tumors of mouse's ovary (Traut and Butterworth), 987
- malignant, effect of pregnancy on (Smith), 616
- ovarian and parovarian, pregnancy complicated by (Wilson), 977
- theca, granulosa and lutein cell, of human ovary and similar tumors of mouse's ovary (Traut and Butterworth), 987
- Twin pregnancy analysis of 521 cases of (Guttmacher), 76
- younger (Fruhlinsholz), 638 (Abst.)

U

- Ureterohydronephrosis resulting from pelvic inflammatory disease (Klempner), 125
- Urethra, female, congenital obstructions of (Stevens), 84 (Abst.)
- lymphogranuloma inguinale of (Gray), 247 (Abst.)
- Urethral sphincter mechanism (Kennedy), 576
- Urinary tract infections, end-results of, associated with pregnancy (Crabtree, Prather and Prlen), 405

- Urine and blood, hormonal studies of, abdominal pregnancy near term, operation and, with placenta left in situ (MacGregor), 1030
- incontinence of (Kennedy), 576
- Urology in women (Lewis), 337 (B. Rev.)
- Uterine adnexa, endometriosis of (Barsony), 419 (Abst.)
- bleeding in preclimacterium, treatment of (Joachimovits), 362 (Abst.)
- hemorrhage, functional, treatment of (Keene and Payne), 688
- prolapse, operation for, an efficient composite, and associated pathology (Richardson), 814
- parametrial fixation operation for (Salmon), 58
- Uterus, bicornuate, unilateral gonorrheal salpingitis in (James), 1045
- body of, cancer of, after irradiation for metrorrhagia (Fournier), 355 (Abst.)
- carcinoma of, diffuse squamous cell (Spielman), 159
- modern treatment of (Dickinson), 355 (Abst.)
- fibroid, pregnancy complicated by, triple diagnostic error in case of (Lucchetti), 1039 (Abst.)
- fundus of, carcinoma of, experience in treatment of (Scheffey and Thudium), 1006
- human (nonpuerperal), effect of ovarian hormones on (Krohn, Laekner, and Soskin), 379
- nonpregnant human, study of contractions of (Robertson), 1047 (Abst.)
- prolapse of (Baer, Reis, and Laemle), 827
- sarcoma of (Novak and Anderson), 740

V

- Vagina of pregnant and nonpregnant women, yeast-like fungi found in (Ch'in and Lim), 266 (Abst.)
- Vaginal discharge (Renton), 1047 (Abst.)
- Vascular factor in toxemias of late pregnancy (Eastman), 549
- Vitosterol and dicalcium-phosphate, bone changes in fetus following administration of, to pregnant mother (Finola, Trump, and Grimsen), 955
- Vlsscher-Bowman pregnancy test, chemical determination of (Drabkin and Goldschmidt), 634
- experience with (Schenck and Tran), 526 (Correspondence)
- Vitamine der Milch (Neuweller), 177 (B. Rev.)
- Von Hippel's disease complicated by pregnancy (Armstrong), 494
- Vulva, carcinoma of, treatment of (Caranza), 357 (Abst.)
- Vulvovaginal mycoses, biologic and clinical import of (Hesseltine), 855
- experimental and clinical therapy of (Hesseltine), 439
- Vulvovaginitis and oral thrush, cultural and morphologic studies of crytococci and monilias isolated from (Hopkins and Hesseltine), 209 (Abst.)

W

- Washington Gynecological Society, transactions of, 529
- Woman, married (Groves and Ross), 341 (B. Rev.)
- single, and her emotional problems (Hutton), 340 (B. Rev.)

The preoperative diagnosis was wrong in 14 per cent. Table III gives the incidence of correct or incorrect preoperative diagnosis and

TABLE III

PREOPERATIVE DIAGNOSIS		INCORRECT DIAGNOSIS	
Correct	78%	Abdominal hemorrhage	2
Suspected	3%	Ovarian cyst	4
Correct after diagnostic curettage	4%	Pelvic inflammatory disease	2
Correct after draining cul-de-sac through rectum	1%	Pelvic tumor	2
		Retrodisplacement and appendix	1
		Acute appendicitis	1
Incorrect	14%	Myopathic bleeding	1
		Ileus	1

the wrong diagnoses are indicated. It would be interesting if we had been able to tell the number of times a diagnosis of ectopic pregnancy was made erroneously.

Of the three deaths, one was due to hemorrhage and shock, the woman being in the hospital but six hours, and five hours after operation. It occurred in 1922, the first year of this series. When she entered the hospital she was almost moribund. Had gum-aeracia been available and more of our modern methods for combating shock attempted immediately she might have been saved. The second woman died on the third day after operation from lobar pneumonia. She had a profuse intraabdominal hemorrhage and was given 800 c.c. of blood by transfusion before leaving the operating table. Recovery from hemorrhage and shock was very satisfactory. The third death was the result of delay in diagnosis, and the refusal of permission for operation when made. The patient left the hospital for five days against advice, signing her own release, only to return in a much more serious condition, and was operated upon two days after the second admission.

In conclusion, we wish to stress the importance of a careful chronologic history of the symptoms and physical and laboratory findings. One should keep in mind the pathology as it appears in the three different phases, namely, before rupture, at the time of rupture, and some time after rupture. Each has its own peculiar picture.

tion of the woman permitted and if the ovary was healthy, the tube was excised, leaving the ovary in situ. Bleeding points on the anterior edge of the broad ligament were caught separately and ligated, after which the upper edge of the broad ligament was sewed over with a fine catgut suture. A wedge of tissue from the uterine horn was included with the proximal end of the tube to obviate the danger of a later ectopic pregnancy in the tubal stump. If the condition of the patient was bad the tube and ovary were removed, controlling hemorrhage by a figure-of-eight suture ligature, taking in the entire upper portion of the broad ligament.

The opposite tube was not disturbed unless it showed sufficient changes to justify it. Other than removing large firm clots which were easily accessible, the removal of blood added to the length of the operation and operative trauma. In none of our cases have we had reason to regret this course, and it is possible that reabsorption of the blood may have been of some value. We found it rarely necessary to use laparotomy pads. Intraabdominal manipulation was minimized to the greatest possible degree. Infusion of gum-acacia in combating shock was a useful procedure prior to or during operation. Transfusion was used in women who were greatly exsanguinated, but not until hemorrhage had been controlled.

Postoperative care was simple. For the first twenty-four hours morphine sulphate was used rather freely and fluids were given as often as indicated.

Other procedures were done in this series as shown in Table II. We do not recommend them. Oophorectomy was done 37 times. Most of these were done as a matter of expediency as mentioned above or because

TABLE II. OPERATIVE PROCEDURES

In addition to removing the pregnant tube the following was done:		
Oophorectomy		37
Single	34	
Both	3	
Curettage		14
Appendectomy		11
Other tube excised		8
Hysterectomy		7
Myomectomy		1
Baldy-Webster operation		1
Defundation		1
Culdesac drainage through rectum		1

the tube could not be excised without destroying the blood supply to the ovary. Appendectomy was done 11 times, but only in women who had very little loss of blood and were in very good condition. Hysterectomy was done 7 times in women who had multiple fibroids or were over forty or for other indicated reasons.

tion and curettage. How far afield one may go in the diagnosis of extrauterine pregnancy is seen in the following list of diagnoses which were either incorrect or did include the extrauterine pregnancy.

TABLE II. DIAGNOSIS

	NUMBER OF CASES		NUMBER OF CASES
Pelvic inflammatory disease, pelvic abscess, or salpingitis	44	Tuberculous peritonitis	1
Abortion	14	Endometrioma	1
Uterine fibroid	13	Placenta previa	1
Twisted ovarian cyst	8	Ruptured varicosities of broad ligament	1
Ovarian cyst	5	Primary anemia	1
Acute appendicitis	4	Carcinoma of fundus	1
Intestinal obstruction	3	Chorionepithelioma	1
Parametritis	2	Carcinoma of ovary	1
Ruptured appendix	1		

The only purpose that can be served in a field already so well covered by the literature, is to remind us for what factors we may look to aid in a more prompt diagnosis.

ETIOLOGY

In the light of our present knowledge, this factor aids but little in the diagnosis of the individual case. Behney¹ suggests that a developmental defect may be inherent in the individual, such as is found in lower animals having extrauterine pregnancy. The occurrence of extrauterine pregnancy decreases with parity; however, Scheffey, Morgan and Stimson² found the reverse true.

Thirty-six per cent of all our patients had never been pregnant previous to the present illness. The other 64 per cent had had one or more previous full-term pregnancies or abortions. It is questionable whether a period of relative sterility is more frequently found in this disease than in other conditions, such as pelvic tumors or gonorrhea. Previous neisserian disease was suspected or proved in 20 per cent of these patients, and complicating pelvic pathology was found at operation in 18 per cent. A previous operation, abdominal or pelvic, had been performed on 15 per cent of all patients.

The youngest patient was sixteen, the oldest forty-three years of age, and 50 per cent of all patients were between twenty and thirty years of age. The presence of etiologic factors not mentioned here is acknowledged. During the five-year period from January, 1929, to December, 1933, there were 54 extrauterine pregnancies as compared with 7,452 abortions, miscarriages, and pregnancies at term, or one extrauterine pregnancy to 138 intrauterine pregnancies. Wynne³ reports one to 303.

THE DIAGNOSIS OF EXTRAUTERINE PREGNANCY

AN ANALYSIS OF 104 CASES

LEON MILLER, M.D., PHILADELPHIA, PA.

(From the Philadelphia General Hospital)

THE literature on ectopic gestation impresses one by the frequency with which this disease is incorrectly diagnosed. Although spontaneous recovery sometimes takes place as exemplified by lithopedions, there is little doubt that delay in diagnosis results in increased mortality and morbidity from this condition. Five of the seven fatal cases in this series were incorrectly diagnosed, and in these five patients the cause of death was undoubtedly the delay in treatment that accompanied the delay in diagnosis, as shown by Table I. The economic loss in the group where an error in diagnosis was made, amounted to an average increase of ten hospital days, or twenty-eight instead of eighteen days per patient. Each of the 104 cases here studied was proved to be an extrauterine pregnancy by laparotomy or autopsy.

Frequently, the disease developed in such a typical manner, that the diagnosis was made by history alone, but in many instances it was reached only after most careful study. Many patients were admitted in shock, or operated upon so soon after admission that complete studies were not carried out. Unfortunately, the operator had often failed to differentiate tubal rupture from tubal abortion, and tubal from extrauterine pregnancy; these differentiations, however important, are omitted. The grossly ruptured cases numbered 88, or 83.3 per cent of the total, and only one of the 16 unruptured cases was correctly diagnosed, a not unusual occurrence. In some patients, rupture had apparently occurred so long before admission that infection had already taken place, thus giving a confusing clinical picture. In other instances, complicating pathology, such as uterine fibroids, ovarian cysts, or pelvic inflammatory disease, helped obscure the underlying pathology.

TABLE I. ILLUSTRATING REDUCTION OF MORTALITY WITH PROMPT TREATMENT

PREOPERATIVE DIAGNOSIS	TIME INTERVAL FROM ADMISSION TO OPERATION		DIED	PER CENT OF TOTAL 104 CASES
	LESS THAN 72 HR.	MORE THAN 72 HR.		
Correct	92%	8%	0	35
Suspected	55%	45%	2	35
Incorrect	19%	81%	5	30

Seven of these 104 patients had been previously examined at this or other institutions and discharged without operation, or after a dilata-

described it as very severe; many attacks followed physical exertion. Sudden weakness and syncope concurrent with the pains occurred in 33 per cent of all cases, but not with all recurrent pains.

Vaginal bleeding was present in 80 per cent of all patients, and varied from a pink tinge to spotting or flooding. Its frequency alone as an initial symptom cannot be too greatly emphasized. Three patients described a chocolate colored discharge.

Urinary symptoms were present in 18 per cent of patients, and consisted of lower abdominal pain and burning before micturition.

Gastrointestinal symptoms consisted mainly of pain in the rectum and abdominal pain on defecation; also marked constipation. Nausea and vomiting was, for the most part, induced by the abdominal pains and occurred in 42 per cent of cases. A few presented the morning nausea and vomiting of pregnancy.

Physical findings of most interest are the abdominal and pelvic; these, however, by their diversity challenge satisfactory discussion. For comparative purposes the various physical findings are best shown in Table VI. It is of interest to note

TABLE VI. COMPARATIVE FREQUENCY OF ABDOMINAL AND PELVIC FINDINGS

	NUMBER OF CASES	PERCENTAGE
Abdominal tenderness (unilateral or bilateral)	93	90
Pelvic mass	80	77
Softened cervix	43	41
Enlarged uterus	23	22
Evident free fluid in abdomen	21	20

that 86 per cent of the pelvic masses palpated were extremely tender, which fact probably aided in the frequent incorrect diagnosis of pelvic inflammatory disease.

Temperature records of the entire 104 cases showed 31 patients, or 29.4 per cent, with an elevation of over 100° F. on admission, or before operation. Seldom did the temperature exceed 102°, and then for only a few hours.

Blood pressure determinations roughly followed the severity of the hemorrhage and were not unusual in this respect.

Blood counts: Table VII shows the relative frequency of preoperative leucocytosis in extrauterine pregnancy. After a comparison, in individual cases, of the leucocyte

TABLE VII. THE LEUCOCYTE COUNT IN ECTOPIC PREGNANCY

90 cases with preoperative leucocyte count	100%
5-10,000 W.B.C.	44%
10-15,000	34%
15-20,000	8%
Over 20,000	14%

count, with the pathology found at operation, and also the preoperative temperature record, the conclusion was drawn that the leucocyte count is more misleading than it is helpful in the diagnosis of ectopic pregnancy. The reverse is true, however, for the erythrocyte counts. Table VIII shows that 75 per cent of all patients who received a preoperative erythrocyte count had a definite anemia of less than 3,500,000 erythrocytes. This is of definite diagnostic value where no great amount of external hemorrhage has occurred, and no prolonged suppurative process has been present.

Sedimentation rate: The blood sedimentation rate was unfortunately done in only 10 cases out of 104. It would be incorrect to base any conclusions on this small

SYMPTOMS

Initial Symptoms.—Those first noted by the patient were invariably some combination of missed catamenia, abdominal pain, vaginal bleeding, and sudden weakness with syncope. Table III shows the relative frequency of their occurrence. The initial symptom followed the last noted menstrual period by an interval of from one day to thirteen weeks, the average being 5.2 weeks. A further study of this phenomenon was productive of no conclusion other than that the first, fourth, and eighth weeks showed the greatest frequency for onset.

TABLE III. RELATIVE FREQUENCY OF INITIAL SYMPTOMS

	NUMBER OF CASES	PERCENTAGE
Missed period (1 or more)	82	79.0
Abdominal pain	59	57.0
Vaginal bleeding	52	50.0
Syncope	11	10.5

It is understood that a past history of menstrual irregularity devaluates a missed period as a symptom; however, 79 per cent of all our patients had missed one or more periods, and of these, 85 per cent had had a past regular menstrual phase. The frequency of amenorrhea is more clearly shown in Table IV.

TABLE IV

PERIODS MISSED	NO. OF CASES	PER CENT
0	22	21.0
1	38	34.6
2	34	32.9
3	10	9.6
4	2	1.9

} 79%

Sixteen of the 22 patients with no missed period had mistaken an irregular or unusual flow for their last normal period.

It is interesting to note the time interval between the onset of symptoms and the patient's admission to the hospital (Table V).

TABLE V

	NO. OF CASES	PER CENT
Admitted within 48 hours of onset	15	14.4
Admitted within 2 weeks of onset	35	33.6
Admitted after 2 weeks of onset	54	51.9

From this it is seen that only 15 patients were admitted within forty-eight hours after the onset of their symptoms, and as expected, 13 of these 15 patients experienced abdominal pain as the initial symptom; 7 of these 13 patients fainted, concurrently with the pain.

Later symptoms than those designated as initial were numerous, and often clouded the clinical picture.

Abdominal pains recurred in 82 per cent of all patients and were the most common symptom, as well as the most variable in severity, location, and type. Pain radiating to the shoulder tops has been noted by Rubin and others. In this series, 11 patients noted severe pain radiating to the right or both shoulders; other areas of radiation were to the lumbar region, rectum, vagina, groin, knee, and epigastrium. Forty-five per cent of the patients described the pain as unilateral; 85 per cent

THE STATUS OF BIOMETRY IN ENDOCRINE DIAGNOSIS

SAMUEL GORDON BERKOW, M.D., PERTH AMBOY, N. J.

(From the Out-Patient Endocrinology Department of the Mount Sinai Hospital)

WHEN Pierre Marie, in 1886, described anatomic changes produced by pituitary disease, he confirmed clinically John Hunter's contention that "structure is the ultimate expression of function." In the same decade, Sir Francis Galton established the use of statistical methods for the study of biologic problems. Since then, the phenomenal rise of endocrinology has focused medical interest on the body form, and biometrics has earned an important place in biologic research. As physicians became increasingly familiar with certain abnormal forms and recognized their association with specific endocrine disturbances, or with glandular syndromes, it followed naturally that many efforts were made to replace this observational and descriptive knowledge by a more precise quantitative technique.

Few researches have seemed so promising initially as these efforts to provide a clinical yardstick for the measurement of man in health and disease. Yet it cannot be denied that the arduous, persistent, and repeated labors of the biometricians have added surprisingly little to the scientific study of abnormal body forms or to their earlier detection. This paper proposes to discuss briefly certain features of the statistical attempts which may have a bearing on their failure and which may have the positive virtue of indicating another and more feasible approach.

* * * * *

Quantitative methods for the study of mankind through physical measurements, though many and diverse, have but two major objectives. First, from measurements of individuals to arrive at mathematical groupings, and hence at generalizations concerning man in the mass. Second, to develop a quantitative technique for the purpose of adding to our knowledge of men and women as individuals.

The first objective does not lie wholly in the realm of medical science. Anthropology has a primary claim. Indeed, this use of the statistical method has proved a perfect tool for anthropology. Physical anthropology owes its existence to the technique of anthropometry.

Medicine has tried to apply the same methods in much the same way and to a similar purpose. The medical objective has been to prepare various "panels" of typical form and function. Against this background of "biotypes" it hoped to isolate the individual, or patient; to

TABLE VIII. THE ERYTHROCYTE COUNT IN ECTOPIC PREGNANCY

88 cases with preoperative erythrocyte count	100%	
1.5-2.0 million R.B.C.	7%	} 75%
2.0-2.5	19%	
2.5-3.0	26%	
3.0-3.5	23%	
Over 3.5	25%	

number. Out of 10 sedimentation rates performed, 6 were faster than 30 mm. in sixty minutes. Each of these 6 cases was found to be grossly ruptured at operation.

Scheffey, Morgan and Stimson² conclude that "the chief value of a sedimentation rate is to differentiate an unruptured ectopic pregnancy from pelvic inflammatory disease. In a ruptured ectopic pregnancy the sedimentation rate is as rapid as in pelvic inflammatory disease."

Biologic test for pregnancy: Not a single patient in this series received a biologic test for pregnancy. Goldberger, Salmon and Frank⁴ in a recent paper, showed their results with the Friedman test in extrauterine pregnancy, in which 32 per cent of all cases gave an incorrectly negative test. They conclude that the test is of value only when positive; a negative test has no value in extrauterine pregnancy.

Colpotomy: A posterior colpotomy or needle puncture was performed on 19 patients, or 18.2 per cent of the total. Blood clot or fluid was obtained in every case, and each proved to be a bleeding ectopic pregnancy. This substantiates the value of the procedure in all questionable cases, and its more frequent use would no doubt have materially lowered the percentage of missed diagnoses in this series.

CONCLUSIONS

1. The incidence of missed diagnoses in ectopic gestation can be materially lowered by an evaluation of all clinical and laboratory findings in each case, always keeping in mind the possibility of an ectopic pregnancy.

2. The mortality rate of ectopic pregnancy can be lowered by a more accurate diagnosis and prompt treatment.

3. Laparotomy is the treatment of choice.

4. There is no unfailing history, symptom, or sign in ectopic gestation.

5. The erythrocyte count is as important as the leucocyte count in this condition.

6. Every gynecologic diagnosis where the erythrocyte count is less than 3,500,000 per c. mm. should include the possibility of extrauterine pregnancy.

7. A posterior colpotomy or needle puncture is of great diagnostic value.

Grateful appreciation for assistance in preparation of this paper is extended to various members of the gynecologic staff of the Philadelphia General Hospital, and to Dr. Charles A. Behney.

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height *and* weight measures is somewhat more significant, and still greater significance is achieved by introducing age into the equation (age—height—weight ratio). The introduction of relationship results from the endeavor to obtain significance. But past a certain point relationship measures become complex, and finally lose sight of their objective entirely.

Several such unwieldy methods have been offered to the medical profession. These misconceptions result in stillborn offspring which become embalmed in the voluminous literature of biometrics.

The limitations of the statistical method are not alone responsible for this failure. If this instrument (valuable in other fields of medicine or allied to medicine) has not been adapted to the direct detection of abnormal body forms or to their more critical study, it must be apparent that the reason for this must lie in the subject also.

From this standpoint, the failure of statistical methods to provide an accurate classification of endocrine or constitutional "biotypes" may be attributed to the fact that there are no *typical* endocrine or constitutional disturbances of the body form.

Hereditary abnormalities have a natural tendency to die out and disappear from the population. Chances for survival, in the generic sense, of the constitutionally inferior person are actually poor, and relatively (that is, compared with the normal person's) almost negligible. Hereditary types or races of constitutionally or endocrinologically abnormal persons simply do not exist.

Also, abnormal forms are not characteristic of specific growth disturbances only, but are determined to a very great extent by the time in the epigenetic development of the individual at which the growth disturbance happened to occur. For example, rhondrodystrophy fetalis and rickets are caused by the same factors operating at different stages of endochondrial growth. The cretin, the hypothyroid and the myxedematous person differ greatly through the same endocrine disturbance occurring at various stages of development.

Conversely, different causes may produce similar abnormalities of form. It is stated, for instance, that "syringomyelia may give rise to the typical clinical and anatomical features of acromegaly" (Fischer, quoted by Swale Vincent). Precocious puberty of pituitary, suprarenal, and ovarian origin cannot be differentiated by means of the altered body form.

So-called abnormal "types" are, therefore, only deviations of form produced by various circumstances which, among other things, interrupt the normal evolution of the bodily symmetry. This leads us to conclude that no system of measurements can resolve the abnormal body forms into an etiologic pattern, or determine by the application of normal standards the causative factors of disease.

identify, to classify, and to study him with instruments of mathematical precision, borrowed from the technique of physical anthropology but renamed *biometry*.

But the attempt to classify mankind into definite physical and constitutional types has not been conspicuously successful. Although this endeavor has intrigued medical minds from the time of Hippocrates, and before, the clinical evidence, admittedly inexact and circumstantial, has hardly been improved by the labors of biometricians. Various measurements have produced only a variety of designations. Compare such types as the asthenic and hypersthenic, "Hochwuchs" and "Breitwuchs," hyperontomorphs and meso-ontomorphs, herbivorous and carnivorous, vegetative and animal, linear and lateral. It is evident that only the labels have been changed. The pigeonholes are the same.

The addition of further measurements, and hence of more complicated panels, has resulted in confused backgrounds, without adding anything useful in the evaluation of clinical problems.

No one will dispute the assertion that this use of biometry has not served medical science as handsomely as anthropometry has served its parent science. When we inquire into this difference, we find that it lies in the fact that the precise knowledge gained from the use of statistical methods pertains to the group and to the group's attributes, and not to the individuals who compose the group. Anthropology—"the science of man"—deals with the individual only as a member of a group. The anthropologist is satisfied to compare groups, whereas the physician desires group statistics (or panels) only for the purpose of diagnosis; that is, for predicting the condition of an individual.

The essential difficulty of such groupings, from the clinical viewpoint, has been that groups derived from few and simple measurements are too inclusive, and those derived from complex measurements become hopelessly involved, overlapping, and inconclusive.

The second objective of the statistical method is represented by such measurements as those of height and weight, stem length, head circumference, chest circumference, etc. These standards were raised through the measurement of large numbers of individuals already classified as to age, sex, race, geographic distribution, general health, and nutrition. Despite their admitted deficiencies when applied to the individual for the purpose of deciding his "normality," the value of such measurements cannot be questioned. Can they be elaborated sufficiently to be utilized in the diagnosis of constitutional and endocrine diseases? Before we answer this question, several facts must be considered.

Standards of this nature are of value only to the extent that they are the measures of a specific and significant trait. Obviously, the most specific measurements are single measurements, such as height alone or weight alone, but these are of slight significance. A combination of

remarkably constant, when deviations produced by age and sex are taken into account. An almost perfect inverse relationship exists between head proportion and age. Measurements of over 400 children six to fourteen years of age (Kiddie Keep Well Camp, Middlesex County, New Jersey) place the coefficient of this correlation at -0.861 . The age progression has been studied from the fetal period (Klein and Scammon) through postnatal development (Meeh, Putiloff, Pfaundler, Kastner, Bardeen, Wörner, Berkow) (Fig. 1).

The abnormal forms are considered without reference to their causation, merely as interruptions of the normal time-sequence in the evolution of the body's architecture. The following examples illustrate this use:

CASE 1.—J. C., female, cretin, twenty-five years of age. Proportions (per cent): head 10.4, trunk 40.5, upper extremities 16.2, and lower extremities 32.4 (thighs 15.3, legs 10.4, feet 6.7). These proportions are normal for a seven-year-old child. J. C. would therefore be considered, from her body proportions, as a case of arrested development in childhood (aged seven). This contrasts with the earlier classification of "typical cretin," which our data did not justify. Mongols, for instance, show a similar arrest of development in surface area proportions.

CASE 2.—D. M., female, aged eighteen, primary amenorrhea (pituitary neoplasm). Proportions: head 8.0, trunk 33.1, arms 14.0, hands 4.3, thighs 19.8, legs 14.0, and feet 6.4. Classification from proportions: development arrested at eleven to twelve years of age (prepubertal proportions).

TABLE I

ABNORMAL DEVELOPMENT	TIME
1. Arrested 2. Retarded 3. Accelerated 4. Precocious puberty	Neonatal cycle
5. Absent 6. Delayed 7. Heterosexual (Not represented in disturbed proportions)	Juvenile phase Pubertal cycle
8. Mixed forms 9. Retarded growth, with normal proportions 10. Accelerated growth, with normal proportions	Adult phase

In the present classification, normal proportions are used as a physiologic time-table through which we can determine the time of origin of the abnormal body forms, that is, the period of development in which the individual began to deviate from the normal proportions (Table I). Although the reorganization of our data has not been completed, it is safe to say that this quantitative knowledge, which can be derived from the measurement of a specific trait (the bodily proportions), is of some clinical importance.

The precise knowledge furnished by biometrics can be of clinical value, but only indirectly, when guided by preliminary research to the measurement of a specific and important trait.

* * * * *

In the past nine years, in the Endocrine Clinic of the Mt. Sinai Hospital, under the direction of Dr. Robert T. Frank, I have had an opportunity to determine the proportions of a large number of individuals exhibiting various endocrine and constitutional disturbances. Thorough clinical and laboratory findings were available. In a paper published in 1932, I reported a statistical classification of a certain part of this material, and attempted to coordinate the statistical groupings with the clinical and laboratory findings.

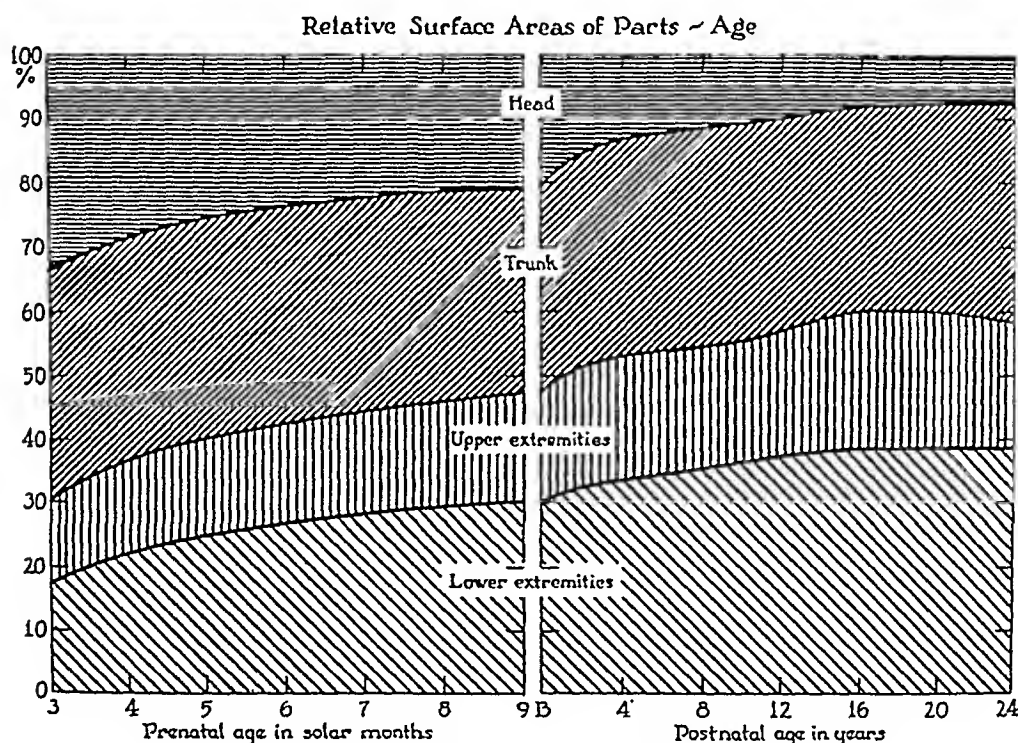


Fig. 1.—Proportionate parts of the surface area of the body. (From E. Boyd, *The Growth of the Surface Area of the Human Body.*)

While a certain degree of relationship was observed, it soon became evident to me that the results, discounting their value as basic data, did not justify the efforts expended on obtaining them. This disillusionment led, for one thing, to a critical review of statistical methods as applied to diagnosis of constitutional and endocrine disturbances, and so to the conclusion that no system of measurements can be applied directly to the diagnosis of endocrine or constitutional disease.

As a further consequence, these data are being reorganized solely on the basis of the age progression of the bodily proportions.

Exact studies have indicated that the proportions of the principal divisions of the body (head, trunk, arms, hands, thighs, legs, feet) are

right paramedian incision the peritoneum was opened and 3,500 c.c. of serosanguineous fluid aspirated, whereupon a tumor measuring approximately 10 cm. in diameter was found attached by a pedicle to the left adnexal region. This mass, apparently a tumor of the left ovary, was very friable, had many hemorrhagic areas and a tear in the upper portion of its capsule. The pedicle of this tumor was clamped close to the uterus, and the tumor and the left fallopian tube were removed. The other ovary was inspected and appeared normal except for several small cystic areas. The uterus was enlarged to about the size expected at puberty. There were no peritoneal transplants and the regional lymph glands were not enlarged. The abdomen was closed without drainage.

The patient made an uneventful convalescence. On the third postoperative day a bloody vaginal discharge was noted for the first time.

The urine was entirely negative except for a two-plus sugar, undoubtedly due to intravenous glucose. The red blood count was 4.93 million, the hemoglobin 70 per cent, the white blood count 10,500, and the differential count was: polymorphonuclear neutrophils 71 per cent, lymphocytes 18 per cent, monocytes 4 per cent, metamyelocytes 10 per cent. On May 25, a barium enema failed to reveal any evidence of organic disturbance. Films taken of the lung fields and sella turcica on June 9 were also negative for evidence of pathology. Through the generous courtesy of Betsy McKennon and Samuel Glass of the Hormone Assay Laboratory, estrogenic hormone tests were made as follows:

DATE	NUMBER OF C.C. OF URINE	MOUSE UNITS OF ESTRIN	MOUSE UNITS OF ESTRIN PER 100 C.C.
5/26/36	23	400	1739
5/28/36	190	200	105
6/ 1/36	490	20	4
7/ 7/36	580	20	3
8/18/36	410	None	None
9/ 1/36	1040	10	1

Eight hundred and fifty-five cubic centimeters of ascitic fluid obtained at operation contained 5,000 M.U., and 80 gm. of the 255 gm. tumor contained 400 M.U.

The pathologic report was as follows: the specimen consisted of a tumor mass measuring 11.5 by 8 by 4.8 cm. and weighing 255 gm. Its external surface was smooth and consisted of a rather thin capsule which had been torn in several places. There were numerous dilated blood vessels just beneath the capsule and the surface varied in color from light gray and pink to dark brown. There were many soft apparently cystic areas, the larger of which measured 3.5 cm. in diameter. On cross-section, in daylight, the tumor was lemon yellow in color and contained numerous cystic areas which varied in size and shape. Certain portions were rather firm to palpation, the largest of which measured 9 by 6 cm. Other portions were much softer, even brainlike in consistency. In addition there were several small areas of hemorrhage and necrosis.

Microscopically, the general impression was that of a highly malignant, anaplastic growth, resembling a gland-cell carcinoma. Trabeculae of a very cellular type of fibrous tissue with spindle-shaped cells separated larger and smaller groups of the epithelial cells. The epithelial cells varied greatly in size and shape with cytoplasm which stained poorly and was not easily seen. The nuclei stained prominently and were of a vascular appearance with distinct chromatin granules, and many of the cells contained fairly prominent nucleoli. In shape the nuclei were round, oval, or of somewhat irregular outline. One feature of note is the immense size of some of the nuclei which were intensely hyperchromatic and contained

GRANULOSA CELL CARCINOMA OF THE OVARY IN A CHILD OF THREE YEARS AND NINE MONTHS

MILFORD X. ANDERSON, M.S., M.D., AND EVERETT A. SHELDON, M.D.,
LOS ANGELES, CALIF.

(From the Department of Surgery, Los Angeles County Hospital)

THE patient, P. H., entered the hospital on May 25, 1936, at which time she weighed 46 pounds, was 42½ inches in height, and three years, nine months, and eight days old.

The present illness began four days before entry with epigastric pain for which she received an enema without noticeable relief. A rather profuse, white vaginal discharge was then noticed for the first time. During the next three days the abdominal pain subsided and she developed progressive abdominal swelling and was brought to the hospital.

The patient was born spontaneously at term, Aug. 17, 1932, weighing 10 pounds, 3.5 ounces and measuring 22 inches in length. She was breast fed for six months and received supplementary feedings of S. M. A. during this time. She did not



Fig. 1.—Photograph taken three days postoperatively, showing the length of the patient 42½ inches, average height of child at five years.

gain very rapidly at first, and at eighteen months of age, her parents felt that she was smaller than normal. During the last year she has grown quite rapidly, especially during the last six months. In February, 1936, the child was taken to the family physician because her breasts appeared larger than normal; this was not very noticeable, however, until she had measles, during the latter part of March. Since then her breasts have increased in size rather rapidly.

Physical examination revealed a very well-developed and well-nourished white child of stated age, having above average intelligence and having the facies of a child at puberty or older. The abdomen was markedly distended and there was dullness over the dependent portions with a shifting area of tympany. A fluid wave was palpable. Peristalsis was active and borborygmi were present. Rectal examination failed to reveal fecal impaction, the cervix and uterus felt larger than normal, and there seemed to be an indefinite mass on the left side of the pelvis. The external genitalia were larger than normal, and there was a moderate amount of white vaginal discharge. Pubic and axillary hair were absent.

At this time a tentative diagnosis of granulosa cell carcinoma was made. As the patient was not improving under conservative management and appeared definitely worse on May 26, immediate operation was performed. Through a lower

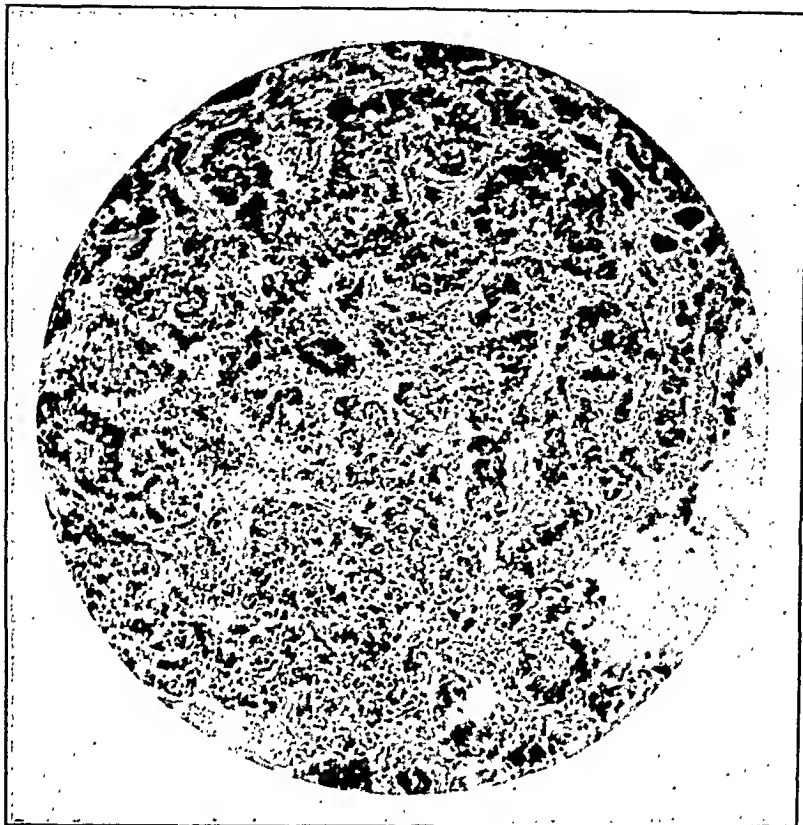


Fig. 4.—Granulosa cell carcinoma. Area showing cylindroid structure. $\times 70$.

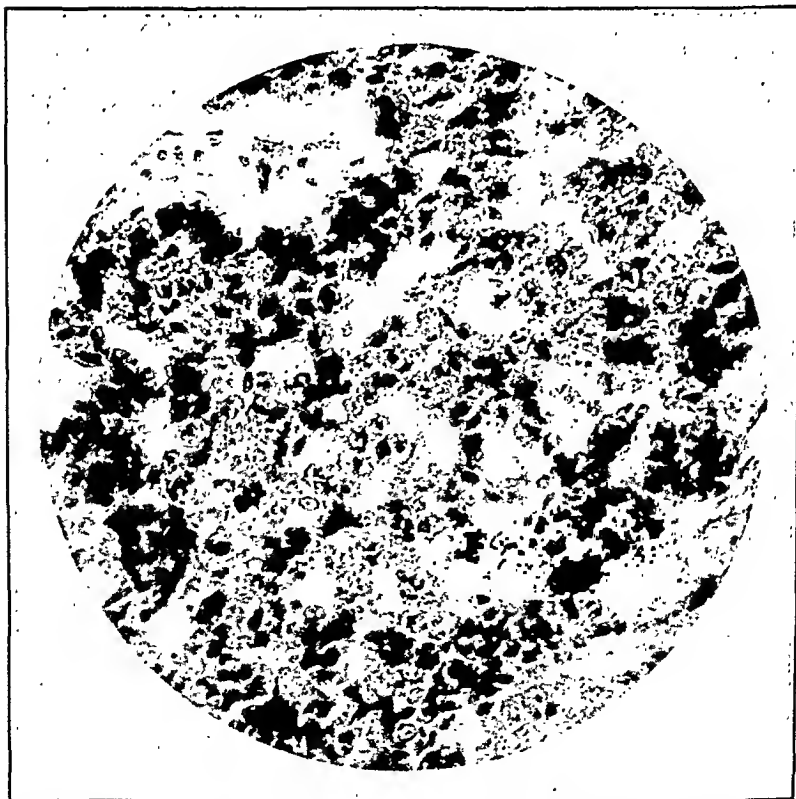


Fig. 5.—Granulosa cell carcinoma. Area showing folliculoid structure. $\times 260$.

bizzare-shaped nucleoli. Mitotic figures were numerous. Microscopic study of the pattern of the epithelial groups gave the impression of a characteristic but vary-

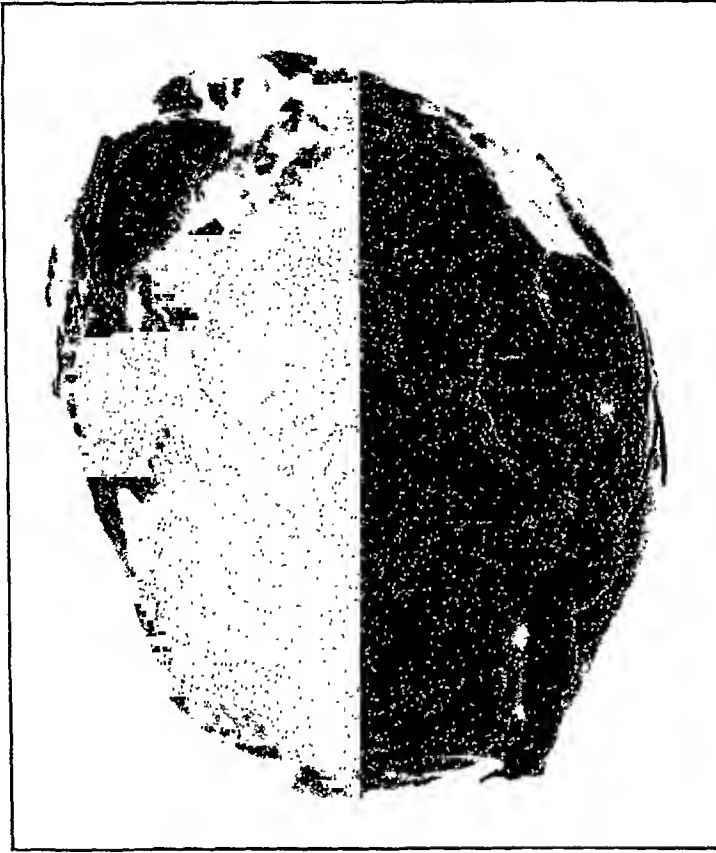


Fig. 2.—Ovarian tumor showing the fallopian tube along right margin.



Fig. 3.—Tumor, bisected, showing numerous cystic areas with firm tumor tissue at the sides and necrotic tissue at the bottom.

ing arrangement. Most of the cell groups had a tendency to exhibit a follicle-like arrangement. These follicles were round, oval, or irregular in outline with a

found in the pelvic and abdominal peritoneum as well as in the mesentery and omentum. The larger nodules in the pelvis as well as some in the region of the incision were removed. The mass of tumor tissue removed at the second operation aggregated a total diameter of 8.5 by 8.5 by 3 cm.

Microscopic: The tumor tissue from the pelvic masses resembled the structure of the ovarian tumor removed at the first operation. It differed, however, in several respects, particularly in the practically complete absence of follicle-like structures. The nuclei were large, the cells were arranged in large homogenous groups, resembling more the sarcomatous or parenchymatous type of arrangement. Many of the nuclei were extremely large and hyperchromatic.

Microscopic Diagnosis: Granulosa cell carcinoma (Newton Evans).

DISCUSSION

The tumor had apparently been present for at least five months, as the mother had consulted a physician about the breast enlargement during February. This would suggest that the tumor was rather slow growing and failed to produce symptoms other than abnormally rapid body growth and precocity (Fig. 1) until the episode of abdominal pain occurring four days before entry. This probably corresponds to the time of rupture of the tumor capsule, which was followed by a rather rapid onset of ascites which is found in only about 10 per cent of cases.² Spontaneous rupture of a granulosa cell carcinoma was found in only two cases^{3, 5} by Thornton⁶ and this was accompanied by bloody ascitic fluid in each case.

In a review of 150 cases Bland and Goldstein¹ found only 8 under the age of ten, the youngest being a patient of Clarence B. Ingraham and Chesmore Eastlake of Denver, reported by Novak,⁴ a child three years and eleven months of age. This would place our case in the lowest age group as she was three years, nine months, and eight days old at the time of operation and precocious development had been noticed at least five months prior to this time.

Although estrogenic hormone tests on the blood would have been of value, it was thought inadvisable as the patient was in poor condition both preoperatively and postoperatively. In place of this the estrin content of the ascitic fluid and urine was tested.

The decrease of urinary estrin, in spite of a recurrence of the carcinoma, was rather surprising. The only explanation we can offer is that the x-ray therapy was probably sufficient to destroy part of the estrin-forming properties of the tumor but not sufficient to inhibit the growth of the cells.

Between Sept. 29, 1936, and Nov. 17, 1936, the patient received 4,900 roentgen units of x-ray at 200 K. V., 7 M. A. at 50 cm. through 0.5 mm. of copper, and 1 mm. of aluminum, which was given in 100 and 150 roentgen unit doses.

The patient died at home Dec. 20, 1936, and an autopsy was not obtained.

We are indebted to Dr. Newton Evans, Chief Pathologist of the Los Angeles County Hospital, for his assistance in the study of this case.

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granular or homogenous content. The small follicle-like structures suggested the primitive graafian follicle. There were less numerous large cystlike openings with a fairly well-organized capsule, which may be compared with the developing graafian follicle. While the greater part of the epithelial groups have this follicle-like structure, some fairly large areas had a quite uniform distribution of the cells, an arrangement called by some "parenchymatous," by others "sarcomatous." A third fairly characteristic arrangement in some areas was that of a coarse network of cords or columns of the tumor cells interspersed with trabeculae of fibrous tissue. In certain areas there was extensive necrosis of the centers of the cell groups and in places rather large necrotic areas involving all of the tumor structures, and infiltrated with blood.

Tentative Diagnosis.—Granulosa cell carcinoma (Newton Evans).

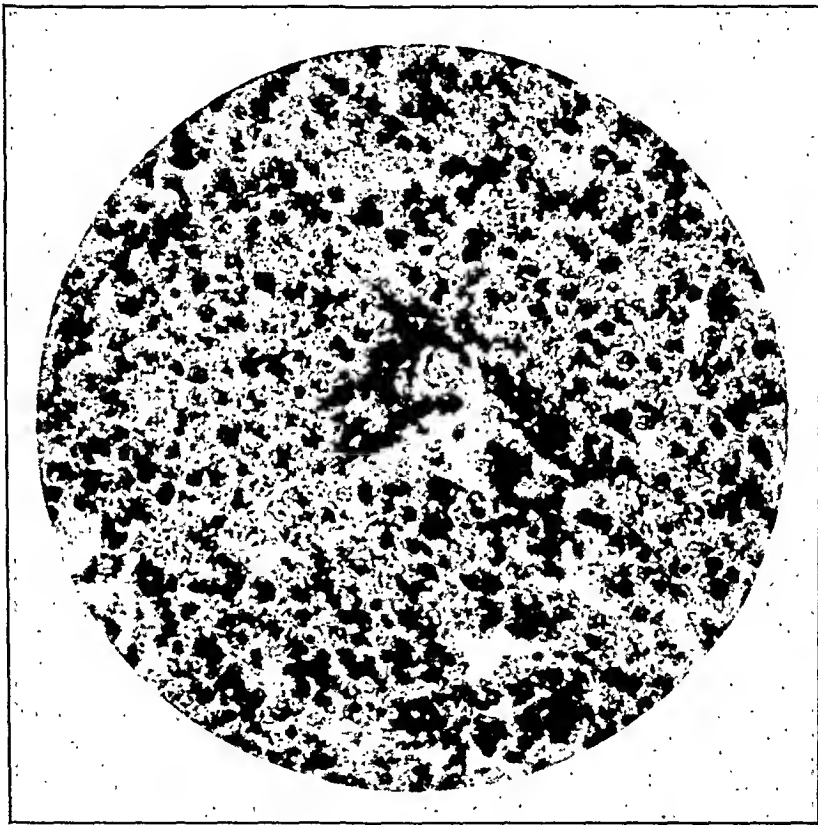


Fig. 6.—Granulosa cell carcinoma. Area showing parenchymatous or sarcomatous arrangement of the cells. $\times 220$.

The patient was discharged from the hospital in good condition on the eighteenth postoperative day (June 13). During the following week she had a small amount of bloody vaginal discharge on one day only. The leucorrhea gradually decreased.

The patient received 900 roentgen units from June 22 to June 29 given in 150 roentgen unit doses daily at 184 K. V., 7 M. A. at 50 cm. through 0.5 mm. of copper and 1 mm. of aluminum.

The patient was followed in the outpatient clinic where it was noted that the breasts decreased to about one-half the former size. However, on August 13, several small nodules were palpated in the region of the right ovary, the largest of which was about 2 cm. in diameter. These nodules increased in size until the patient was re-admitted (Aug. 27, 1936). In spite of a recent negative estrin test of the urine, a laparotomy was performed and numerous metastatic nodules were

12 c.c. on the left; microscopic examination of the specimens obtained was negative; indigo carmine appeared in fair concentration in six minutes from the left side and rather weaker from the right; urine cultures were negative. Phenolsulphonephthalein excretion showed less than 10 per cent in four hours. The blood urea nitrogen was 9 mg. per cent. Repeated concentration tests showed definite, marked impairment of function, inability to concentrate above 1.010. Intravenous pyelography showed definite marked bilateral ureterohydronephrosis, the calyces being particularly distended and the upper portion of each ureter similarly involved (Fig. 3). The Frei test was negative.

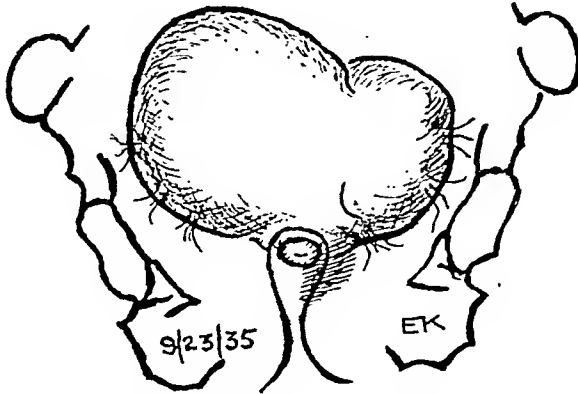


Fig. 1.—Pelvic findings Sept. 23, 1935.

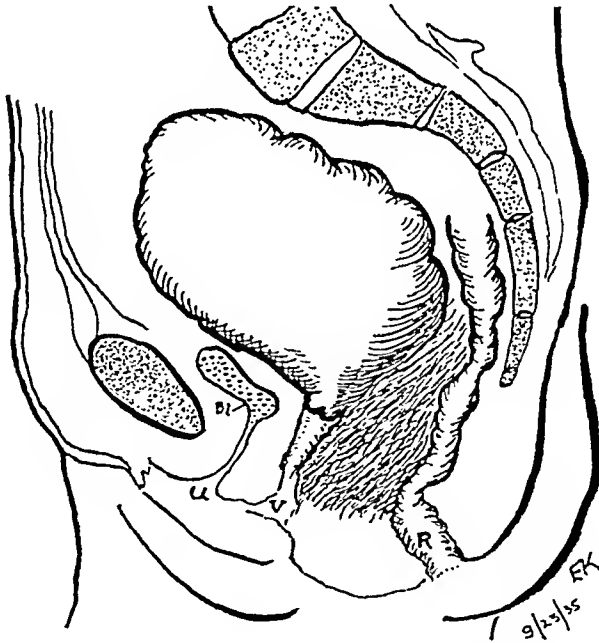


Fig. 2.—Pelvic findings Sept. 23, 1935.

DISCUSSION

The medical consultants were of the opinion that the severe impairment of renal function was due to ureteral compression, on a mechanical basis, and that there was no primary parenchymal lesion of the kidney. The evidence of impaired renal function and the dilatation of the upper urinary tracts appeared due to the pelvic inflammatory process. Under

URETEROHYDRONEPHROSIS RESULTING FROM PELVIC INFLAMMATORY DISEASE

EMANUEL KLEMPNER, M.D.,* NEW YORK, N. Y.

(From the Gynecological Service of the Mount Sinai Hospital)

URETEROHYDRONEPHROSIS associated with neoplasms of the pelvic organs has been reported frequently. Pregnancy also has been stressed as an etiologic factor. Pelvic inflammatory disease, however, rarely has been found to be the cause of ureterohydronephrosis. The following unusual case is therefore presented.

CASE 384782.—R. K. The patient was a twenty-four-year-old American-born housewife. Her only pregnancy two and one-half years previously had ended in a stillbirth in the eighth month, following an injury to the abdominal wall. Her menses had always been irregular, the interval varying from three weeks to three months, the duration four or five days. Two years before admission to the hospital the patient noticed a vaginal discharge. Her physician informed her that she had "an inflammation in the pelvis." In the three months preceding admission to the hospital the patient suffered recurrent lower abdominal pain associated with occasional nausea and vomiting. During this time she had lost sixty pounds in weight. In the two months preceding her admission she had noticed urinary frequency and urgency with occasional incontinence.

Physical examination on admission to the hospital revealed a pale, obese, chronically ill-appearing young woman. Blood pressure was 110/70. The general examination revealed no abnormalities except a large, hard, lower abdominal mass appearing to arise from the pelvis and reaching to within one fingerbreadth of the umbilicus.

Pelvic examination showed a densely hard, irregular mass, reaching on the right almost to the level of the umbilicus and slightly lower on the left. The uterus and adnexa could not be identified separately from this mass. On rectal examination a definite obstruction to the finger was encountered two inches from the anal orifice. This was caused by a dense, hard, annular constriction infiltrating and fixing the rectovaginal septum completely. The mass was densely adherent to the pelvic walls and gave the impression that one was dealing with a "frozen pelvis" (Figs. 1 and 2).

Laboratory studies showed hemoglobin 80 per cent, sedimentation time fourteen minutes, white blood count 13,000 with 76 per cent polymorphonuclear leucocytes, and blood Wassermann four-plus on two occasions.

The diagnostic possibilities that presented themselves were: (1) a pelvic inflammatory process with perirectal constriction; (2) a pelvic malignancy, either primary or secondary; and (3) lymphogranuloma with perirectal infiltration. Further studies were undertaken to establish the diagnosis.

Barium enema revealed an irregular stenosis of the rectosigmoid ascribed to extrinsic pressure. It was impossible to pass the sigmoidoscope beyond the narrow, angulated rectum. Cystoscopy revealed the bladder capacity to be diminished to 160 c.c.; the bladder was distorted and appeared as an elongated, elevated, tubular structure with the trigone somewhat displaced to the left; both ureters were catheterized to the kidney pelves, and there was retention of 14 c.c. on the right and

*Joseph Brettauer Research Fellow in Gynecology.

observation the pelvic mass showed some tendency to diminish in size. Because of this and in view of the impaired renal function, it was considered wiser not to attempt intervention, which necessarily would be hazardous, but to treat the patient conservatively. Accordingly, anti-syphilitic therapy was instituted and the patient has been closely followed during the past sixteen months.



Fig. 5.—Intravenous pyelogram Feb. 10, 1937.

During this period there has been a marked improvement in the patient's condition. She has gained weight. Her hemoglobin has risen from 60 per cent to 88 per cent. The sedimentation time has increased from fourteen minutes to one hour, twenty minutes. Phenolsulphone-phthalein test shows more than 30 per cent of the dye excreted within four hours. A concentration test now shows that kidney function has

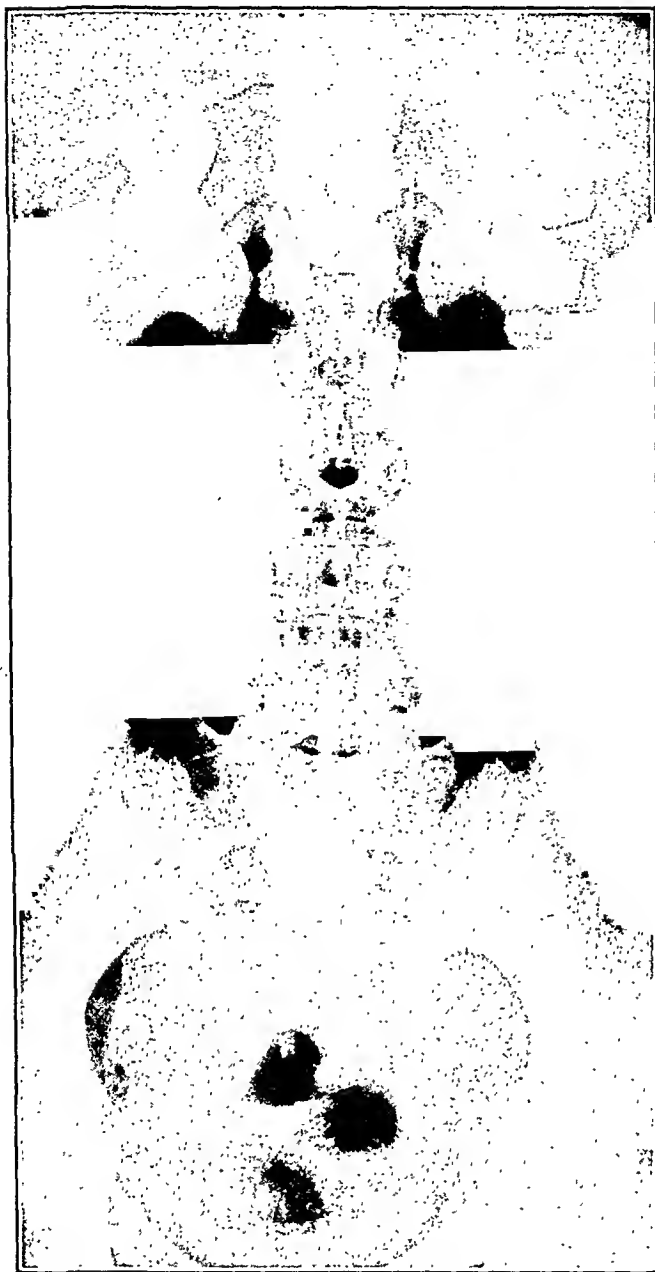


Fig. 3.—Intravenous pyelogram April 17, 1936.

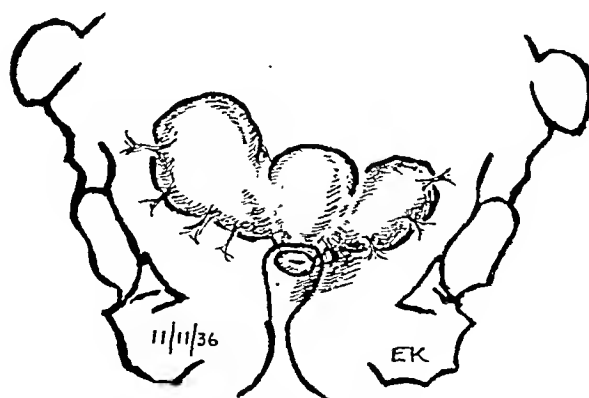


Fig. 4.—Pelvic findings Nov. 11, 1936.

MASSIVE PUBERTY HYPERTROPHY OF THE BREASTS

JOSEPH A. GAINES, M.D., NEW YORK, N. Y.

(From the Laboratories and Gynecological Service of the Mount Sinai Hospital)

RECENT hormone studies relating to the physiology of breast development have stimulated renewed interest in the etiologic factors responsible for certain pathologic alterations of that organ. Among these aberrations, the massive enlargement of the breasts seen in puberty hypertrophy is particularly striking. Such a case in a fourteen-year-old girl is presented, with a description of the pathologic anatomy and a discussion of its probable hormonal relationship.

As is well known, the female breast may show normal and rather wide variations in size at any age after puberty, depending upon the individual, the presence of a gravid state, lactation, or obesity. Infrequently, enormous hypertrophy may develop, the breasts in some instances reaching almost to the knees. This abnormal growth has been variously termed virginal, puberty, puberal, massive diffuse, or nongravid hypertrophy. Although cases have been described with the onset at a mature age or during pregnancy, they are usually seen at puberty, shortly before or after the menarche. Enlargement may continue with a varying degree of velocity from several months to two years. The first case was recorded by Durston⁷ in 1669, in which the left breast weighed 64 pounds and the right 40 pounds, the greatest hypertrophy yet reported. On the average, however, a single breast approximates seven to ten pounds in weight. Bilateral involvement is usual, and slight differences in size not infrequent. The hypertrophy is diffuse, giving rise to enormous, pear-shaped organs. The rapid expansion results in a thinned skin, flattened nipples and enlarged areolae. Local circulatory disturbances are the rule, and include distended, tortuous, superficial veins, chronic edema and a tendency to ulceration of the skin. The gross and microscopic features described in the case reported are representative.

CASE REPORT

P. G., a fourteen-year-old girl, was first admitted to the Endocrinological Clinic of Dr. R. T. Frank in February, 1936, because of excessive enlargement of the breasts. Her birth and childhood development had been normal in all respects. Menstruation began at the age of thirteen, sixteen months prior to admission. The menses recurred regularly, at first every twenty-one days, and later every four weeks for three to six days. The flow was moderate, without dysmenorrhea. Before the onset of the menarche the breasts were described as not different from those usually observed in early puberty. With the beginning of the menses, however, both breasts rapidly enlarged and reached their maximum size at the end of four months. From

markedly improved, as evidenced by the ability of the kidney to concentrate up to 1.018 in comparison with the previous level of 1.010. A normal-sized uterus with bilateral adnexal masses can now be felt. The pelvic mass has diminished in size though the infiltration of the recto-vaginal septum still persists. The pelvic mass is now somewhat movable in comparison with its previous dense adherence to the pelvic walls (Fig. 4). Intravenous pyelogram (Feb. 10, 1937) shows a definite decrease in the ureterohydronephrosis particularly on the left side (Fig. 5).

It has been interesting to follow this unusual complication in a common disease and to note the improvement under a conservative regime.

69 EAST 90TH STREET

Courtois, J., Longuet, A., and Lecoq, R.: *The Rôle of Avitaminosis in Coli Bacillus Infections of Pregnancy*, *Gynécologie (Paris)* 35: 216, 1936.

According to the authors disturbances in the female sex hormones predispose to acidosis. The presence of vitamins in general and vitamins A and B in particular plays a very important rôle in pregnancy. Lack of vitamin A increases the tendency to acidosis. The absence of vitamin A diminishes the defense of the villus epithelium and favors infection, particularly infection due to the colon bacillus. Exogenous and endogenous factors may also result in colon bacillus infections during pregnancy. The exogenous factors usually arise in the alimentary tract. Alkalosis like acidosis may favor the development of a colon bacillus infection, but alkalosis is extremely rare in a pregnant woman whereas acidosis is unusually common. With this knowledge it is easy to overcome colon bacillus infections during pregnancy. The means consist of overcoming alkalosis or more commonly acidosis by the administration of phosphoric acid or sodium bicarbonate. Likewise, there must be an abundant supply of vitamins A and B. In some instances saline injections are necessary and in others a serum or vaccine may help.

J. P. GREENHILL.

Kraus, J.: *Diabetes Mellitus and Pregnancy*, *Med. Klin.* 32: 375, 1936.

Before the advent of insulin a pregnancy in patients with diabetes mellitus was rare, because of severely regressive changes in the follicle apparatus of the ovaries which led to amenorrhea and sterility. The probable cause for this is diminished function of the hypophysis.

In most cases the diabetes antedates the pregnancy. First appearance of diabetes during pregnancy is rather uncommon. Before the introduction of insulin, pregnancy was a serious complication of diabetes.

During the latter part of pregnancy, there is less danger from diabetes but there is an aggravation again after labor and during the puerperium.

Since the use of insulin the maternal mortality has dropped from limits between 27 and 55 per cent to 17 per cent. One danger of insulin is hypoglycemic coma. In spite of insulin the fetal death rate still is about 43 per cent. Furthermore, a large proportion of these children die during the first few weeks of life. Many children born of diabetic mothers are overweight which is due to the hyperglycemia of the mother. When insulin is used most of the babies have a normal weight.

J. P. GREENHILL.

breast was composed of firm, white, fibrous tissue, divided by thin septa into lobes of varying size. The gross impression was that of a diffuse overgrowth of all elements of the breast, but especially of the fibrous tissue component. Some portions appeared softer and more edematous than others. Scattered, punctate, translucent areas corresponded to the epithelial structures within the connective tissue matrix. No distinct, encapsulated fibroadenomas were noted, although these have been described not infrequently in puberty hypertrophy.

Microscopically, there was marked hyperplasia of the duct and lobular structure and surrounding connective tissue stroma. The individual lobules represented a stage of development which could be classified as unripe, compared with that seen in the normal adult, and corresponded to the picture usually encountered at the age of puberty (Fig. 2). The lactiferous ducts were large, elongated and lined by epithelium in two layers. Within the lobules the terminal ducts appeared slightly dilated. Fine divisions of the ductules, either as blunt, clublike, solid thickenings or partially opened alveoli could be seen. These, however, were relatively infrequent, in conformity with the picture normally encountered at the patient's age, in early lobular development. The distribution of glandular elements was not entirely uniform, being numerous in some areas and sparse in others. The interlobular connective tissue, composed of coarse, collagen fibers, seemed particularly abundant. Moderate edema and vascularity were present. A distinct differentiation existed, for the most part, between the inter- and intralobular stroma. The latter (the mantle connective tissue immediately about the clusters of ductules, epithelial buds and acini) contained fine collagen fibers and appeared more cellular and loosely arranged, with occasional lymphocytes.

Endocrinologic Studies.—The following studies were performed in the Endocrine Research Laboratory. Ten grams of the hypertrophied breast tissue were extracted for female sex hormone and found negative. An assay of 15 gm. of the tissue did not show the presence of gonadotropic hormone. Examination of the entire urinary excretion over a period of one month for the anterior pituitary gonadotropic factor revealed no abnormal findings. The total urinary excretion of female sex hormone in twenty-four days was determined at 1,720 mouse units, which is within the limits of normal. A study of daily vaginal smears through a month's cycle showed no abnormal features.

DISCUSSION

An evaluation of the factors that might possibly be responsible for the massive hypertrophy illustrated in this case must take the following into consideration: (1) the histologic and pathologic changes occurring in normal breast development with special reference to the time of puberty, (2) the relationship of various hormones to growth of the breast.

At birth both the male and female breast contains an elementary system of large ducts with some branching, but no lobule or acinus formation. From birth to puberty there is a period of relative quiescence, growth being limited mainly to an elongation of the ducts (Loeb²⁵), with only moderate division, sufficient to keep pace with the general development of the body. With puberty in females, the mamma receives an added impetus and there follows a rapid and progressive dichotomous division of the milk ducts. The terminal portions especially show numerous solid, epithelial buds which become hollowed out into small tubules, and

then until the time of examination, one year later, there was no increase in size, but rather a lengthening and narrowing of the breast pedicles. The patient experienced a dragging sensation in the chest and a feeling of tenseness without pain. The child was disturbed mainly because of the unsightliness of her figure. During the last few months, small ulcerations appeared at the site of the constricting bands of a specially constructed breast support. These healed slowly. No subjective changes were experienced during the premenstrual or menstrual phase. Five months before admission she received four x-ray treatments to the breasts at another hospital, without, however, any apparent improvement. The family history revealed no evidences of any unusual breast abnormalities. The past history was negative.

The general appearance, aside from the local condition, was that of a bright, well-proportioned young girl of fourteen years. No deviations from the normal were noted somatically. Both breasts showed extreme, pear-shaped enlargement down to below the level of the umbilicus (Fig. 1). There was some asymmetry, the left being larger than the right. The areolae appeared enlarged, and the nipples inverted.

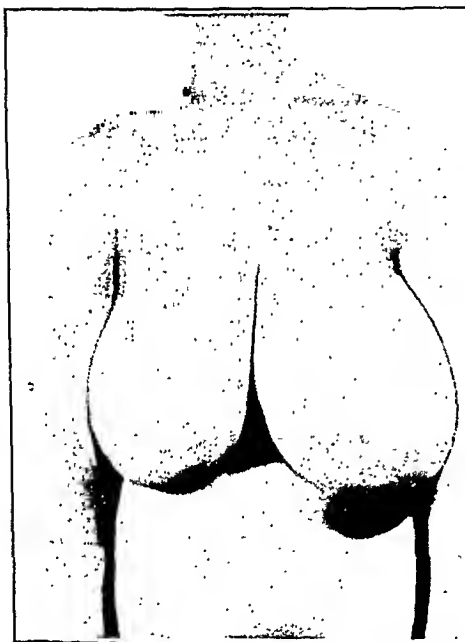


Fig. 1.

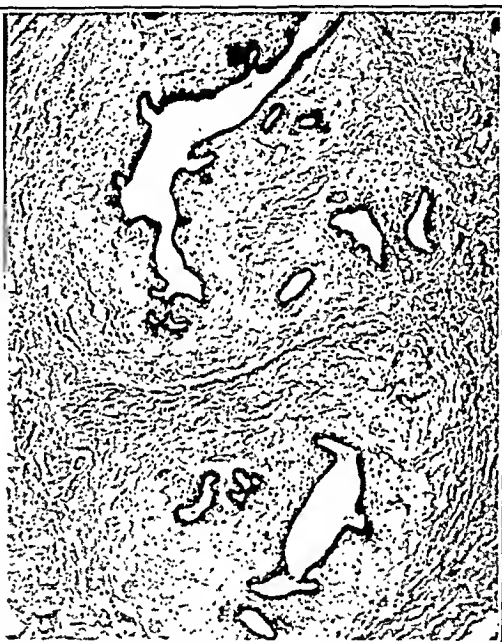


Fig. 2.

Several distended superficial veins were seen to course from the base of the mamma. Palpation revealed a moderately firm and uniform consistency.

Anthropometric measurements were essentially normal. The height was 60½ inches and the weight 114 pounds. Hematologic studies were entirely negative. Urine examination revealed no abnormalities. The basal metabolism was -15 per cent. X-ray examination of the sella turcica showed it to be normal in size and shape. The blood Wassermann test was negative.

In March, 1936, the patient was admitted to the Surgical Service of Dr. H. Neuhof. A bilateral simple mastectomy was performed in two stages. It was thought unwise to attempt preservation of the nipple area. Instead, a small, conical portion of the breast tissue was retained on each side to form the basis of two small, artificially constructed breasts. Healing proceeded uneventfully with an excellent cosmetic result.

The resected breasts were similar in appearance. The left weighed seven, and the right, four pounds. Beneath the thin, stretched skin, several, large distended veins were apparent. Practically no fat tissue was present. The hypertrophied

treated hypophysectomized and intact castrated rabbits with estrogenic and corpus luteum hormone. Similar breast development resulted in both groups. Using hypophysectomized and intact male guinea pigs, Nelson corroborated the above findings. Male rabbits previously treated with theelin show a definite increase in size of the breast after the injection of the galactopoietic hormone. This, however, is not due to any further growth of the ductal system, but rather to the distention of the preexisting system with secretion. In intact male or ovariectomized female guinea pigs, the use of the ovarian hormones not only causes mammary development, but on their removal initiates the onset of lactation (Nelson²⁹). He believed that the removal of the inhibiting influence of the estrogenic hormone on the anterior pituitary lobe permits the lactogenic hormone to act. In hypophysectomized guinea pigs, however, this effect is not obtained, nor will lactation continue in animals after the hypophysis is removed. The dependence upon the pituitary gland for initiation and maintenance of lactation is thus indicated.

The convincing experimental evidence of the direct dependence of the breast upon the ovarian hormones for growth permits a correlation of the normal stages of human breast development with the endocrine studies already made. In early childhood, when the undeveloped breast is quiescent, Frank has found little or no pituitary gonadotropic or female sex hormone in the blood or urine. At puberty or prepuberty a cyclic excretion of estrogenic substance has been demonstrated by Frank⁸ and by Fluhmann,¹³ though definitely less than in the mature woman. In one nine-year-old girl, four mouse units per liter of urine were found. In another twelve-and-one-half-year-old girl, one-half the adult amount of female sex hormone was recovered two and one-half months before the menarche. At this time the previously rudimentary mamma shows pronounced growth activity in the glandular tissue and surrounding stroma. In the normally menstruating, maturing girl definite blood and urinary cycles of gonadotropic and female sex hormone are present, and the breast shows a lobular structure which slowly increases in complexity until the adult stage is reached. After the complete menopause the quantity of estrin falls markedly and breast atrophy ensues. During pregnancy when the increase in estrin, progesterin, and the pituitary hormones is marked, there is a proliferation of the acini and dilatation of the ducts in addition to the lactogenic effect. In two cases of precocious puberty, due to the presence of a malignant ovarian tumor, female sex hormone was recovered from the urine (Frank^{8, 10}). These children showed premature development of the secondary sex characteristics, including enlargement of the breasts. Heidrich and his coworkers²⁰ report a case of teratoma of the testis with gynecomastia. Two hundred and fifty mouse units of female sex hormone were obtained from a liter of urine, and 35,000 mouse units of gonadotropic hormone.

then lengthen to form further subdivisions. Thus, a definite lobular structure composed of branching small ducts and finely calibered ductules is formed. There is an absolute and relative increase in both the loose, mantle connective tissue which ensheathes the duct system and in the general supporting stroma of the breast. The terminal end portions of this arborized system may be lined by a single or double layer of epithelium. They are, however, distinctly different from the single layered, dilated acini in the lactating lobule. According to Dieckmann⁶ the increase in size and complexity of the lobule continues until the "adult lobule" is produced. The extent and rate at which this takes place varies with the individual and accounts for the variety of pictures encountered at any particular age. Occasionally it may remain at a more infantile level, comparable to infantile genitalia. The quantity of fat tissue within the breast is another variable factor. It becomes especially evident after the onset of puberty and increases with general body adiposity. After mature mammary growth is reached, aside from those changes induced by pregnancy and lactation, the lobular structure remains permanent until menopausal regression ensues.

That a relationship exists between breast development and ovarian function has been recognized for many years. The failure of the breasts to develop following prepubertal complete gonadectomy, and their atrophy after the menopause and operative or x-ray castration pointed in this direction. Grigorieff (1897), Halbau¹⁹ (1900) and Knauer²³ (1900) confirmed this view by their successful implantation of ovarian tissue in young castrated animals, with resultant breast development. Steinach³² also was able to induce mammary growth in male guinea pigs by ovarian transplantation. In the past few years extensive experimental work has indicated that the estrogenic and corpus luteum hormones are responsible for the growth of breast tissue and that the pre-pituitary lactogenic hormone is concerned with milk secretion.

When oophorectomized, adult virgin rabbits are stimulated by injections of female sex hormone there results an extreme overgrowth and ramification of the ductal system of the breast with practically no acinar growth, the pattern resembling that of a barren, branching tree (MacDonald²⁷). If, however, the estrogenic hormone in combination with progestin is used, both a ductal and acinar overgrowth occur, giving rise to well-developed gland lobules with numerous alveolar outbranchings from the terminal ductules. The employment of a corpus luteum hormone alone has no effect. Hypertrophy of the breast with growth of the duct system after the injection of estrin has been noted by numerous investigators in the male cat, the male guinea pig (Turner and Gomez³⁴), castrated rabbits and guinea pigs (Gardner, Gomez and Turner,¹⁵ MacDonald²⁷), and mice (Gardner, Smith and Strong¹⁶).

To prove that the ovarian hormones acted directly upon the breast and not through the anterior pituitary gland, Asdell and Seidenstein¹

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TRUE HERMAPHRODITISM IN MAN, WITH AN ENDOCRINOLOGIC STUDY*

RALEIGH R. HUGGINS, M.D., MORTIMER COHEN, M.D., AND
BOYD HARDEN, M.D., PITTSBURGH, PA.

(From the School of Medicine, University of Pittsburgh, and the
Elizabeth Steel Magee Hospital)

TRUE hermaphroditism in man is relatively rare. There are many cases recorded in medical literature but only a few can be considered as true proved cases according to the requirements laid down by earlier authors. The proof of true hermaphroditism rests in the demonstration of both ovarian and testicular tissue. Gross evidence is not sufficient, both tissues must be identified microscopically. The gonads need not be present as separate structures, they may be combined as one single body, the ovotestis.

Kwartin and Hyams¹ in 1927 made a critical review of the literature and reported a case of their own, bringing the total number of instances of true hermaphroditism in man up to twelve. Their report included the material presented by Young² in 1933 where he repeated the total figure as twelve in the world's literature. Later in 1933 Stojalowski and Debeski³ reported an authentic case harboring both ovary and testicle. Early in 1936 Warthen and Williams⁴ presented a case with bilateral ovotestis. There have been other reports in the literature entitled true hermaphroditism, but they failed to satisfy the microscopic requirements. McFarland⁵ demonstrated only testicular tissue in an individual who was otherwise a typical female. The tissue was removed at operation for femoral hernia and was later identified microscopically as testis. Urechia and Teposu⁶ showed microscopic sections of uterus and ovary removed at operation from an individual with hypospadias and gynecomastia. They obtained living spermatozoa from their patient and concluded, although in the absence of proved testicular tissue, that their patient was a true hermaphrodite. Morison⁷ presented a case as true hermaphroditism in which only testicular tissue was demonstrated. Warthen and Williams⁴ cite a case by Essenberg and Feinberg, but we cannot locate the reference in the literature. Including the case reported here, the instances of true hermaphroditism in man up to the present time, number fifteen.

*The endocrinologic studies were made possible by a grant from the Buhl Foundation.

Geschickter, Lewis and Hartman¹⁷ interpret the histology of gynecomastia, puberty growth and puberty hypertrophy as being similar. They have produced a typical picture of gynecomastia in the monkey (*rhesus maeaeus*) by injections of female sex hormone.

The weight of evidence points to the conclusion that virginal hypertrophy is an exaggeration of the normal growth changes seen at puberty, that the direct stimulus for breast enlargement at this time is derived from the estrogenic and possibly also the corpus luteum hormone, and finally that these ovarian hormones are concerned in the etiology of massive hypertrophy. In the present case the endocrine studies were normal. It is to be noted, however, that they were done one year after the breasts had apparently stopped growing, so that no definite interpretation can be made. It has been pointed out that the technique of our present methods for the quantitative estimation of certain hormones, though much improved, is at best rather crude. There are several endocrine secretions which cannot be measured or are measured with difficulty. Further, one cannot evaluate the effect of such possible factors as small increases in the circulating hormones over varying periods of time, large increases over shorter intervals, the renal threshold and the local response of the tissues involved.

SUMMARY

A case of puberty hypertrophy of the breasts in a girl of fourteen years is described, including endocrinologic studies. The pathologic anatomy indicates a marked hyperplasia of the glandular and connective tissue elements with preservation of the unripe lobular structure ordinarily encountered at puberty. The hormonal factors responsible for mammary growth are discussed and a correlation made with normal physiologic development of the breast. The weight of evidence indicates that the estrogenic hormone and possibly also the corpus luteum hormone is directly responsible for growth of the breast and is concerned in the etiology of puberty hypertrophy.

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normal and the left gonad was examined grossly and was considered as a normal ovary. The contents of the right inguinal canal were, right tube, anomalously inserted round ligament, and gonad. The gonad was the size of a normal ovary, but had a dark flattened lower pole. Its upper pole was studded with small red protrusions. The right gonad was removed but the right tube, which was considered normal, was left intact. No other structures were removed. The hernial sac was repaired and the abdominal wound was closed. The patient made an uneventful recovery, and five months after operation considered herself a normal female.

Tissue Examination.—The phallus measured 6 cm. in length and 2 cm. in diameter. It resembled a penis with prepuce, glans, and body. There was an

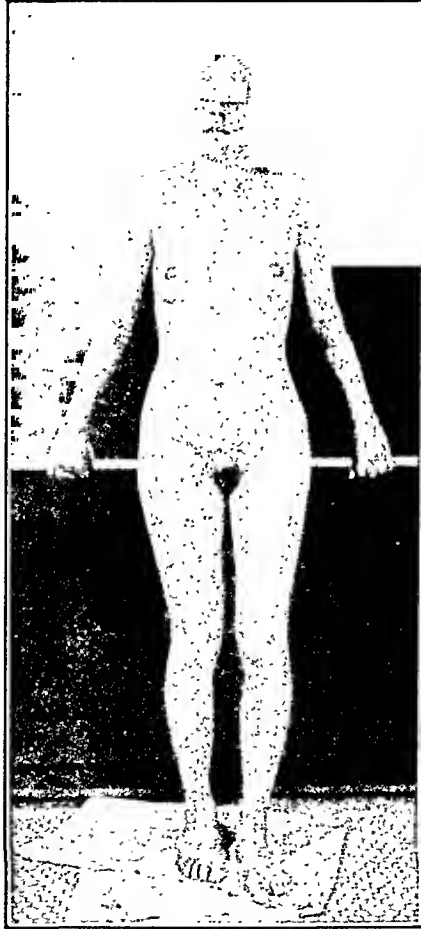


Fig. 2.—Patient after operation.

urethral indentation on the lower aspect of the glans, but no opening was present (Fig. 1). On cross-section two well-defined corpora cavernosa were present surrounded by a dense connective tissue. No corpus spongiosum was seen. Microscopic examination showed typical corpora cavernosa surrounded by a heavy tunica albuginea.

The ovotestis measured $3\frac{1}{2}$ by $2\frac{1}{2}$ by 1 cm. Its upper pole was somewhat broader than its lower pole and the surface was yellow white studded with small red protrusions. The surface of the lower pole had a red cast, and there was a fairly sharp line of demarkation between the two. There was a definite hilar indentation. On gross section the upper pole occupied a little more than half of the entire structure and presented an appearance typical of ovary with small cysts containing

CASE REPORT

Patient (No. 25957), twenty-nine years old, white, was admitted to The Elizabeth Steel Magee Hospital as a female, complaining of an enlarged clitoris which became erect at times, and caused considerable annoyance. Generally "her" health has been good and "she" has been considered a female all her life. The clitoris became enlarged at fourteen. Menses began at fourteen and have been regular each month, lasting for five days, associated with pain and accompanied by soreness and irritation of the clitoris. During school years "she" was rather athletic, and recently "she" has worked as a saleslady. The past medical history and the family history were of no interest.

Physical examination showed a patient 54 inches high, weighing 117 pounds. The general body contour suggested a male figure with relatively broad shoulders and narrow hips (Fig. 2). There was a small amount of fine hair on the upper lip. The breasts were small, with large nipples. The pubic hair was of feminine



Fig. 1.—External genitalia before operation, showing penis and vulva. Note urethral indentation in glans, and swelling in right groin.

distribution. There was a mass that was freely movable and the size of a normal ovary in the right inguinal canal, $2\frac{1}{2}$ cm. from the external ring. The introitus was small and protected by an intact hymen. The phallus measured 6 cm. in length and 2 cm. in diameter. There was a fold of skin, a prepuce, covering the glans (Fig. 1). The urethra was located at the site seen in the normal female. The vaginal vault was smaller and more shallow than normal. The cervix was small, nulliparous in type, and was continuous with the uterus which, while displaced to the right, was of normal size. X-ray examination following lipiodol injection revealed the uterine cavity of normal size and contour. The left tube filled with lipiodol and appeared normal. There was no shadow for the right tube. Routine laboratory examinations gave results within normal limits.

At operation, the phallus was amputated close to the base. The mass in the right inguinal region was reduced into the abdominal cavity and the abdomen opened. The uterus was of normal size, although drawn to the right. The left tube appeared

cells several layers thick, others only a single layer of cells with a thick hyaline tubular wall. Other tubules were completely hyalinized. There were numbers of cell nests which were interpreted as interstitial cells (Fig. 5). Toward the hilar portion there were tubules lined with deep staining epithelium suggestive of rete testis.

ENDOCRINE STUDIES

Estrin determinations were made on the urine according to the method of Cuyler,⁸ with the following results:

3 days prior to operation	3.5 rat units
15 days after operation	9.0 rat units
16 days after operation	11.0 rat units
67 days after operation	16.6 rat units
5 months after operation	5.2 rat units

Androitin determinations were made on the urine according to the method of Cuyler and McCullagh,⁹ with the following results:

3 days prior to operation	5.5 mm. of growth
1 day after operation	5.5 mm. of growth
15 days after operation	2.0 mm. of growth
67 days after operation	0.0 mm. of growth
5 months after operation	0.0 mm. of growth

Blood iodine determinations were made following McCullagh's¹⁰ technic to ascertain any variation in thyroid activity.

3 days prior to operation	8.4 micrograms in 100 c.e. blood
13 days after operation	5.9 micrograms in 100 c.e. blood
14 days after operation	51.0 micrograms in 100 c.e. blood
15 days after operation	30.4 micrograms in 100 c.e. blood
67 days after operation	9.2 micrograms in 100 c.e. blood
5 months after operation	8.6 micrograms in 100 c.e. blood

The abnormal iodine readings found subsequent to operation are the result, probably, of the external application of iodine to the patient's skin in dressing the operative wound.

COMMENT

Theoretical considerations of hermaphroditism with attempts to explain the formation of such anomalies are considered in Kwartin and Hyams'¹ paper where they review the literature on the subject. There have been numbers of detailed descriptions of the external appearances and of the detailed anatomy of hermaphrodites. In certain reports² the sex life of such individuals has been considered, where an individual lived part of the time as a man and part of the time as a woman, marrying an individual of the opposite sex and apparently enjoying a successful marital state in each instance. It is highly possible that such a condition might exist if it be considered that both hormones may be present at the same time. In our case, the female characteristics outshadowed the male and this can easily be explained by the amount of hormone present. Further, the fact that the androitin secretion diminished to zero following removal of the right ovotestis suggests that the left gonad which was not removed at operation is an ovary. It is also interesting that the ovarian tissue microscopically is much more the normal than the testicular tissue which shows atrophic changes. The individual then was more female than male. This is the first report in which both male and female sex hormones have been simultaneously demonstrated in hermaphroditism. Finkler¹¹ made endocrine studies on a pseudohermaphrodite female and demonstrated only traces of estrogenic substances until after treatment when the menses appeared and the estrogenic substance was increased in amount.

watery or pink fluid and bodies resembling corpora fibrosa. The lower pole had a yellow brown striated appearance and threadlike tubules could be pulled from the surface, as from normal testis. Microscopic examination showed the upper pole typically ovary, with primordial follicles, graafian follicles in all stages of develop-

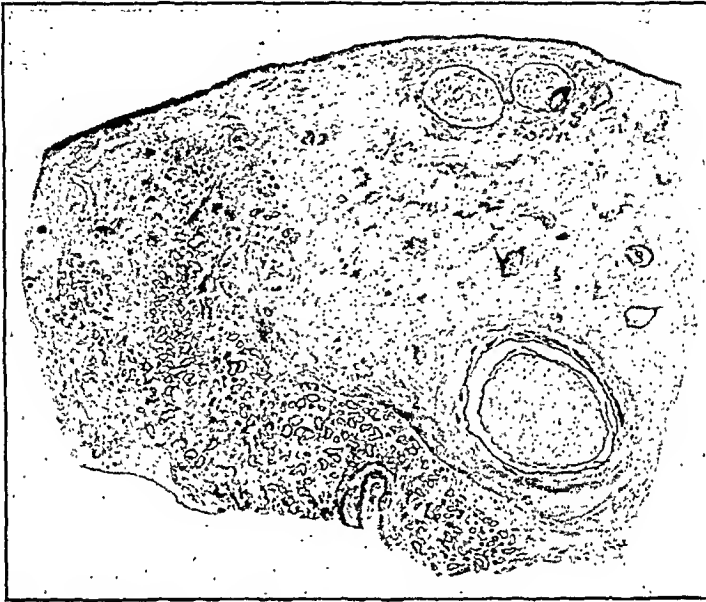


Fig. 3.—Ovotestis. $\times 10$.

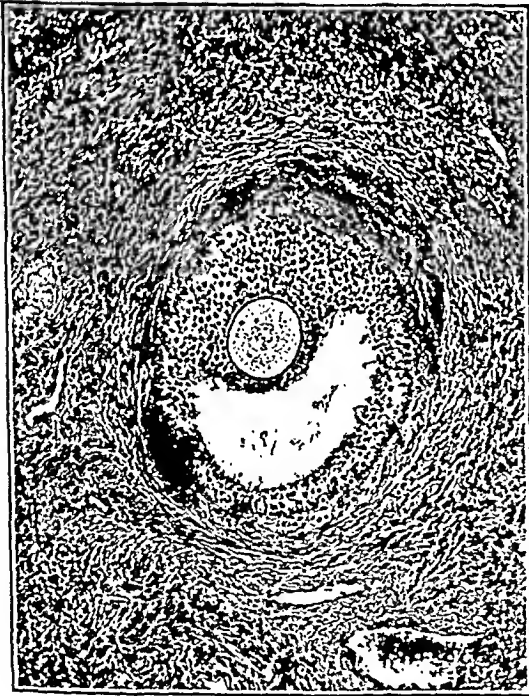


Fig. 4.

Fig. 4.—Maturing graafian follicle. $\times 100$.

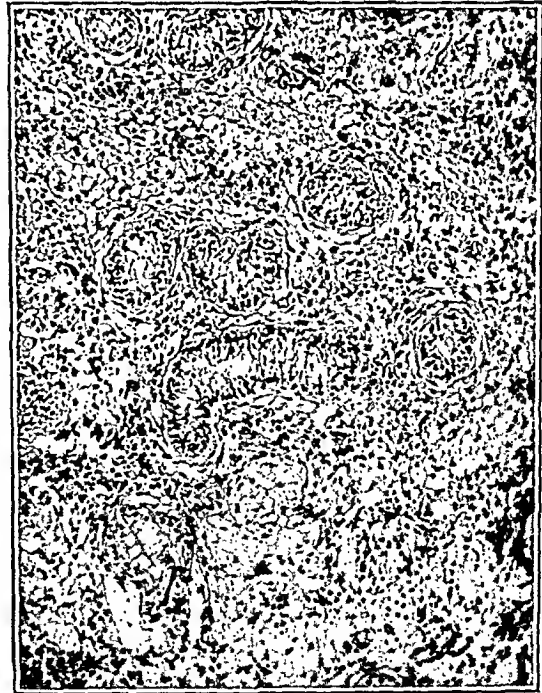


Fig. 5.

Fig. 5.—Testicular tubules partially atrophic. Note loose stroma and interstitial cells. $\times 100$.

ment, corpora hyalinosa, and small cysts surrounded by hemorrhage. The stroma was characteristic of ovary (Figs. 3 and 4). The lower pole was composed of seminiferous tubules in varying stages of atrophy. Some of the tubules contained

THREE CASES OF PLACENTA PREVIA FOLLOWING TUBAL INFLATION

BENJAMIN E. URDAN, M.D., MILWAUKEE, WIS.

DURING the past five years of my private practice, I have seen 120 patients in whom a complete investigation of their infertile marriage was made. One hundred and two patients complained of primary sterility and the remainder of the secondary type. Ninety-eight had some degree of tubal patency, whether normal or partial, judging from their symptoms, fluoroscopy in certain cases, and the kymographic tracings of the tubal peristalsis. Eleven became pregnant the month of inflation or the following month. According to the criteria of Rubin and others, these pregnancies can be attributed to the inflation. Ten of these patients had intrauterine pregnancies and one developed a tubal pregnancy. Of the ten women with intrauterine pregnancies, three developed placenta previa. This occurrence becomes even more unique when it is noted that but one other case of placenta previa has been seen in my private practice.

All three patients with placenta previa were multigravida, this being the fourth pregnancy for one, the third for another, and the second for the last patient. Each had had one abortion. Curettage had been necessary in only one case. All were spontaneous in origin. No placenta previa occurred in any of the seven patients who had never before been pregnant and who became gravid immediately after inflation.

The etiology of placenta previa is conjectural. Arcy¹ states that the determining factors which cause nidation of the ovum and placentation in any particular area in a strictly physiologic pregnancy are unknown. Cilia and muscular action have been held responsible for the transportation of the ovum to its implantation site. There is no reason to believe that the point of entry bears any necessary relation either to the mouths of the uterine glands, which are too small to offer lodging, or to mucosal folds or furrows. In fact, the premenstrual endometrium is swollen and smooth at the time of implantation, whereas foldings are first characteristic of the young gravid state. In man it is impossible to know whether chance or special qualities of the mucosa govern the selection of the site. Conceivably the more pronounced premenstrual changes occurring in the fundus, and especially in the median planes, are significant in view of the predilection for these locations. Perhaps the spot may be lacking in cilia so that the embryo becomes stranded.

Bethel Solomons in 1929 before the British Medical Association said that "a pathological condition of the endometrium is a fruitful cause of placenta previa.

SUMMARY

1. A case of true unilateral hermaphroditism in an adult white person is reported.
2. The phallus and ovotestis were removed at operation, leaving probably normal female internal and external genitalia.
3. Endocrinologic study is presented for the first time in true hermaphroditism with the demonstration of both male and female sex hormones. The male sex hormone disappeared entirely while the female sex hormone increased in amount after operation.

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Moyes, R. E.: The Problem of the Midwifery Services From the Standpoint of the Country Practitioner, Brit. M. J. 2: 386, 1936.

The author describes the home conditions for maternity service that exist in a semiindustrial area in Newcastle-on-Tyne and in North Northumberland. The author is of the opinion that a great deal of harm is being done and undue alarm created among women by the publicity given to maternal mortality in the press. Any improvements in the maternity services of the country generally should be along the following lines: (1) A medical man and a midwife should attend each case. (2) Routine antenatal care for each case. (3) Where necessary, aseptic equipment should be provided, to include blankets, bedpans, dressings, etc. (4) No midwife or district nurse should be allowed on duty with other cases that are suspect or septic. (5) Where necessary, anesthetics should be provided at the expense of the local authority. (6) An emergency service should be established in each area and also a scheme of expert service available for all conditions at all stages.

F. L. ADAIR AND S. A. PEARL.

Massabuán, Guibal, and Joyeux: Ovarian Grafts. The Anatomic Conditions for Conservation of the Ovary in Situ, Gynécologie 35: 449, 1936.

The blood supply of the ovary essentially depends upon the anatomic arcade formed by the two arterial trunks coming from the uterine and the utero-ovarian arteries respectively. Either one of these arteries can supply the ovary with all the blood it requires. Hence ligation of only one of these vessels does not interfere with the nutrition of the ovary. Therefore, the author sees no justification for the complicated operations devised to save the branch from the uterine artery in order to ensure a proper blood supply for the ovary. A salpingectomy may safely be performed without interrupting the blood supply to the ovary. However, the author prefers ligation of the individual blood vessels in the mesosalpinx rather than a mass ligature.

J. P. GREENHILL.

CASE 2.—Hospital No. 76623. Mrs. L. L., aged twenty-four, was seen on Feb. 4, 1935, complaining of relative sterility. Four years previously she had had a spontaneous abortion at two months.

Physical examination was relatively negative, except for a moderate girdle obesity. Pelvic examination was essentially negative. Basal metabolic rate was -2. Study of the husband's spermatozoa revealed that the percentage of abnormal forms was well within the normal range. A reduction diet and small doses of thyroid were given. The patient was next seen on June 5, 1935. She had lost thirteen pounds in weight. Tubal inflation was done and the tubes were normally patent. The patient became gravid during that month, and when seen on Aug. 10, 1935, the uterus was the size of a seven to eight weeks' gravidity. Quickening occurred on Oct. 10, 1935.

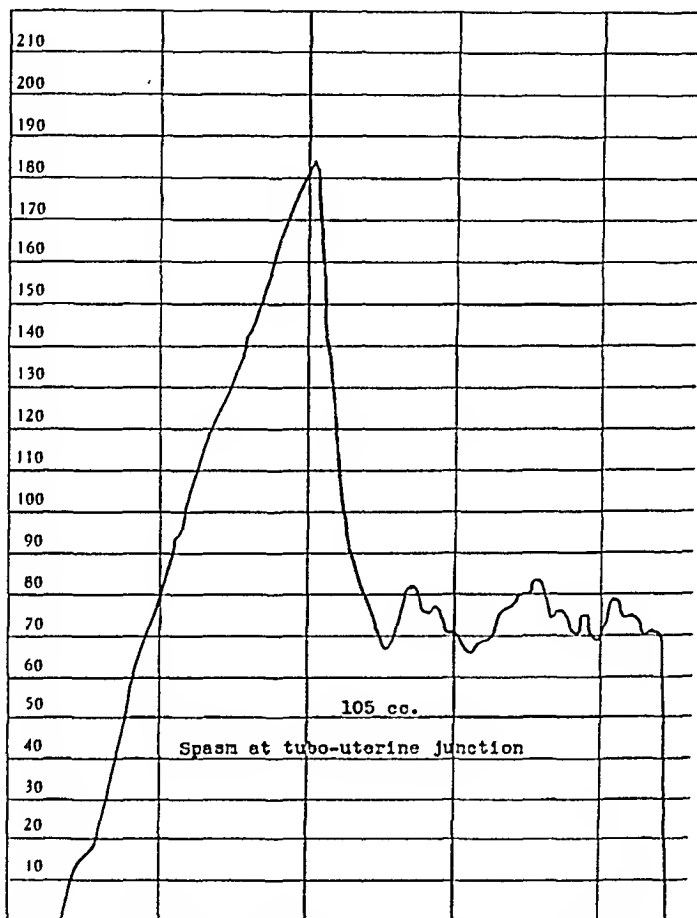


Fig. 1.—Kymographic tracings of tubes of patients who had placenta previa. Spasm at tubouterine junction.

The date of expected labor was about March 6, 1936. On Dec. 9, 1935, when the patient was about twenty-seven to twenty-eight weeks pregnant, she began to spot slightly with no pain. This continued very slightly until December 12 when there was a sudden passage of bright red blood. Total amount lost at this time was about 150 to 200 c.c. She was transferred to the hospital and examination revealed the cervix to be dilated 3 to 4 cm., and the placenta was found covering part of the internal os. The membranes were ruptured artificially and a Voorhees' bag was inserted. Four hours later there was complete dilatation of the cervix, and an infant weighing 13¼ pounds was delivered by version and extraction. The infant died twelve hours after birth. Convalescence of the mother was uneventful.

CASE 3.—Hospital No. 76265. Mrs. L. M., aged thirty-seven, was seen July 23, 1934, complaining of menorrhagia of one year's duration and secondary sterility.

Curettage should be done before the next pregnancy." He stated that there had never been a repeat case in his practice since that procedure had been established.

Solomons and H. E. Canter² believe that placenta previa is caused by a deficient formation of decidua in the upper portion of the uterus with a normal decidual formation in the lower portion. They feel that the deficiency of stroma cells following infection, too frequent labor, etc., and their replacement by fibrous tissue is the reason for the deficient decidual reaction in the fundus. Changes in the endometrium as to diminution of stroma cells occur more readily in the upper portion than the lower with the result that there should be a normal decidual reaction in the lower part of the uterus. From their experimental work they conclude that the deficient decidual reaction in the upper part of the uterus is the cause of placenta previa.

Holmes³ summarizes the etiologic factors of placenta previa as follows: (1) an antecedent endometritis, postpartum or postabortal, or the result of contamination by intrauterine manipulations or other infections, or some pathologic alterations of the mucosa resulting from degenerative changes incident to neoplasm or endocrine disturbances; (2) direct result of the effect of abnormal migrations of the ovum (gravity), overgrowth of the placenta or a reflexal placenta.

No attempt to conclude that tubal inflation was an etiologic factor in the causation of placenta previa can be made here. Two of these patients had normal patency and the other had uterotubal spasm. Each of these patients was a multigravida and one also had fibroids of the uterus. This patient had menorrhagia, but it is doubtful if there were any submucous fibroids as the menorrhagia was controlled by the use of desiccated thyroid. There no doubt had been some antecedent endometrial alteration in all cases. However, it is believed safe to assume that the insertion of the cannula could cause a release of a thickened mucous plug in the region of the internal os and the lower portion of the body of the uterus with the result that the endometrium in this area offered a better nidatory bed for the impregnated ovum than the endometrium in the upper portion of the uterus.

CASE REPORTS

CASE 1.—Hospital No. 76265. Mrs. B. M., aged thirty, complained of secondary sterility. There had been three pregnancies; the first two, forceps deliveries at term, and the third ending in a six weeks' spontaneous abortion. There had been involuntary sterility for the past four years.

The physical examination was essentially negative, as was the pelvic examination. A Hühner test was normal. Tubal inflation was done on Aug. 13, 1934, five days after the cessation of the period. A graph typical of uterotubal spasm was obtained. The patient had shoulder pains immediately upon sitting up. She was seen on Oct. 28, 1934, with a history that her last menstrual period had occurred on Sept. 10, 1934. Friedman test was positive. Pregnancy was marked by a slightly greater weight increase than normal. Her basal metabolic rate was $-8\frac{1}{2}$, and she was given small doses of desiccated thyroid. Quickening was noted on January 20. Date of expected labor was about June 17, 1935. On May the second, the patient spotted slightly and she was put to bed. The spotting recurred again one week and ten days later despite bed rest. She was then hospitalized. The following day she lost about 200 c.c. of bright red blood without any pain. Vaginal examination revealed the cervix to be long and to admit one finger. The placenta was found covering about two-thirds of the internal os. The patient was about thirty-five weeks pregnant. A low classical cesarean section was done and a four-pound, fifteen-ounce male infant was delivered. Both mother and infant left the hospital in good condition.

MENSTRUAL FISTULA (TUBO-ABDOMINAL)

WITH THE REPORT OF A CASE

SEYMOUR WIMPFHEIMER, M.D., NEW YORK, N. Y.

THE occurrence of a menstrual, tubo-abdominal fistula is sufficiently uncommon to merit the addition of such a case to the literature.

Menstrual fistula is a term proposed by Ballin* for a fistula in a laparotomy scar characterized by the periodic discharge of blood, more or less coincident with normal menstruation. He describes two types; namely, those due to direct communication with the uterine or tubal lumen, and those due to postoperative enclosures of endometrial tissue in the abdominal wall. The utero- or tubo-abdominal fistula usually follows an operation for pelvic inflammatory disease, in which partial or complete salpingectomy or partial hysterectomy has been performed. Occasionally it occurs after certain types of operation for ventral fixation of the uterus, especially where nonabsorbable suture material has been utilized. The second type may also follow operations on the uterus and adnexa, during which endometrium may be deposited in the abdominal wall, as in cesarean section.

Although most of these fistulas originate after a surgical operation, there have been reported rare instances of a pyosalpinx or a tubal pregnancy which have ruptured spontaneously through the abdominal wall and resulted in the formation of a fistula. On the other hand, endometriomas arising from displaced müllerian derivatives have also been reported as occurring in the abdominal wall and giving rise to periodic discharge of blood.

CASE REPORT

An eighteen-year-old unmarried woman was admitted to the Beth Israel Hospital on Feb. 19, 1936. She complained of bleeding from an abdominal scar at each menstrual period since July, 1935. Previous to this her menses were normal. She had had an appendectomy in 1934. In May, 1935, the patient, then living in Georgia, noted a yellow vaginal discharge before and after her periods. This was associated with burning on micturition. Her June period was prolonged for thirteen days and was accompanied by severe lower abdominal pain and right costal pain which radiated to the right shoulder. A dilatation and curettage was performed on July 7, at Rome, Georgia on the diagnosis of an incomplete abortion. She was discharged from the hospital after a stay of three days but returned the following day with a temperature of 103° F. A laparotomy was immediately done and both tubes and the left ovary were removed. There was no drainage of the wound. She was allowed to leave the hospital after eight days.

On the second day of her next menstrual period she observed a bluish swelling at the lower end of the abdominal scar. The swelling increased in size, became pain-

*Ballin, M.: Surg. Gynec. Obst. 46: 525, 1928.

The patient had been married for sixteen years and had one full-term delivery fourteen years previously. In 1926 she had had a cervical repair and appendectomy performed. Four years previously she had had a dilatation and curettage for incomplete abortion. A hysterectomy had been recommended because of the menorrhagia and small fibroids.

Physical examination was negative, except for the fact that the patient was moderately overweight and had a mild myxedematous appearance. Pelvic examination revealed the uterus to be slightly larger than normal and slightly irregular on the right side, as though there were several small subserous fibroids. The cervix was clean and normal in appearance. Basal metabolic rate was -12.9 per cent. The Hühner test was normal. She was given small doses of thyroid extract for her hypothyroidism, and iron therapy for her mild secondary anemia. After eight weeks of therapy the patient's general well-being was considerably improved, and her menstrual periods had approached the normal both in duration and in the amount of blood lost. Because of no pregnancy after five months of therapy, a tubal inflation was done on Jan. 11, 1935. The tubes were normally patent. The patient became pregnant immediately. Quickening was felt on May 8. The date of expected labor was Oct. 9, 1935. On Sept. 2, 1935, the patient had slight painless bleeding, bright red in color. She was transferred to the hospital. The bleeding was intermittent on

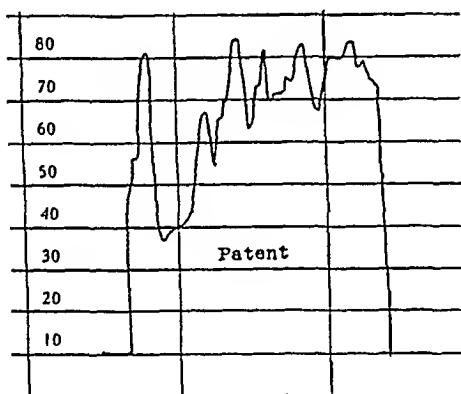


Fig. 2.—Normal patency.

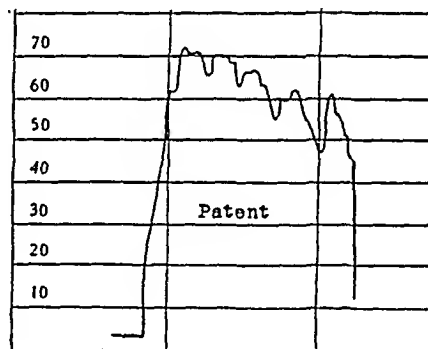


Fig. 3.—Normal patency.

Sept. 3, 1935. There was no bleeding until September 6, when the patient had a painless hemorrhage of about four ounces of bright red blood. Vaginal examination was done and the cervix was found to admit one finger with the placenta covering the entire internal os. The patient was approximately thirty-five weeks pregnant. A cesarean section was performed and the placenta was seen to be completely covering the internal os. A male five-pound six-ounce infant was delivered. The condition of both mother and infant was good. The patient has been examined at frequent intervals and one small subserous fibroid is noted on the right side of the uterus. Menstruation has remained within the normal limits under small doses of thyroid.

SUMMARY

Three cases of placenta previa in women who became pregnant immediately following inflation are reported. All three patients were multigravida with long periods of sterility since their last pregnancies.

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and the fistulous opening was excised down to the fascia. In the subcutaneous tissue, the fistulous tract could not be identified, but when the fascia was exposed, the opening was observed and a probe was inserted for a distance of two inches. The peritoneal cavity was opened. After separation of many dense adhesions between uterus and omentum, the relationship between the fistula and the uterus was established. The right tube and most of the left tube and ovary had been removed at the previous laparotomy. The right ovary was cystic and enlarged to the size of a peach. The uterus was dextroverted, and the fistulous tract was found to go to the stump of the left tube which was situated to the right of the median line. The fistulous tract, the stump of the left tube, and the interstitial portion were removed by a cylindrical excision of the uterine wall down to the level of the endometrium. The opening in the uterus was closed by two layers of buried sutures of chromic catgut. A Lembert suture was used for the serosa. The left round ligament was used to cover over the sutured area by sewing it to the anterior wall of the uterus.



Fig. 2.—Microphotograph (high power) showing the tissue spaces lined by foreign body giant cells simulating epithelial tract.

The patient made an uneventful recovery. The operative wound healed by primary union, and when the patient was last seen eleven months after the operation, her menses were somewhat irregular but there was no recurrence of bleeding from the abdominal scar.

PATHOLOGIC REPORT (DOCTOR A. PLAUT)

A. A strip of skin 14 cm. long and 1 cm. wide. Microscopic section showed chronic inflammation of the subcutaneous tissue. There were present giant cells and pigment. Some giant cells contained highly refractive, partly crystalline, small foreign bodies.

B. Another piece of the specimen was irregularly conical, measuring 4 by 3.5 cm. at the base and 5 cm. in height. The base was formed by muscle tissue and dense fascialike tissue. The uppermost portion was irregularly conical; this portion was

ful, and ruptured spontaneously in three days, discharging bloody fluid. The wound healed over in a few days. For the five months previous to her admission to the hospital, the bloody discharge appeared with each menstruation.

On admission there was an induration one inch in diameter at the lower end of the midline abdominal scar. In the center of this area was a pinpoint opening discharging sanguineous fluid. The uterus was found to be fixed anteriorly. No other masses were palpated. The smear of mucopurulent discharge from the cervix revealed the presence of gonococci. No gonococci were found in the urethral discharge. The complement fixation test for gonorrhea was weakly positive. The Wassermann and Kahn tests were negative. Red blood count was 3,500,000, hemoglobin 70 per cent. The sedimentation rate was normal.

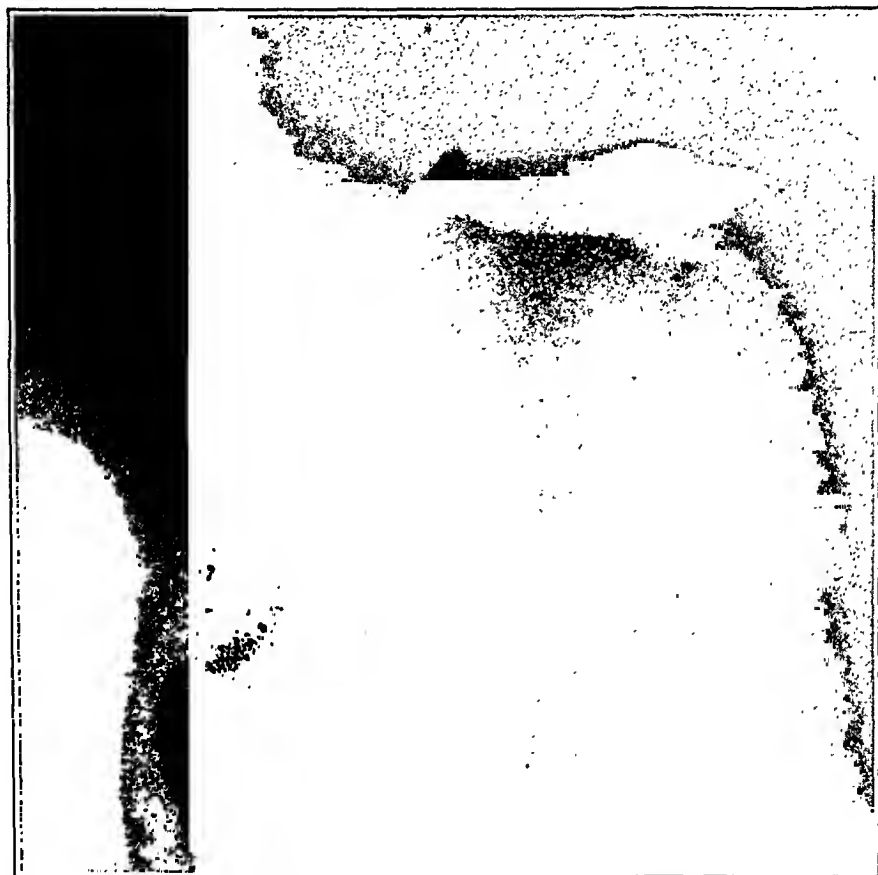


Fig. 1.—Roentgenogram. Lipiodol shadow in uterus, stump of right tube and fistulous tract from stump of left tube to the abdominal wall.

Further diagnostic and therapeutic procedures had to be postponed because of the active gonorrhea. The patient received hyperpyrexia treatment as developed by Bierman and Horowitz for the cure of her gonorrhea. On the day following the treatment and on three subsequent occasions the smears were negative for gonococci. The cervical discharge disappeared.

In order to determine more clearly the true condition, lipiodol was injected through the cervix into the uterine cavity. There was no escape of oil through the sinus opening. The x-ray, however, showed the right tube closed about 1 cm. from the isthmal end and a sinus tract leading from the left tube to the abdominal wall (Fig. 1). The diagnosis was therefore made of tubo-abdominal fistula.

On March 13, I. C. Rubin excised the tract under spinal anesthesia. The operative procedure and findings were as follows: the scar containing the indurated portion

THE USES AND LIMITATIONS OF ROENTGEN PELVIMETRY

HERBERT THOMS, M.D., NEW HAVEN, CONN.

WITHIN the last fifteen years obstetrics has seen the development of a number of roentgen methods for measuring the bony pelvis. The advantages in obstetric practice of possessing information regarding the dimensions of the pelvis are obvious, and it is also true that such information must leave no doubt as to its accuracy. The chief methods in vogue today are accurate to the degree necessary for all obstetric purposes, and certain stereoscopic methods, although requiring a good deal of special technique and apparatus, not only appear reliable but are quite striking in their portrayal of the pelvis.

With the experience gained from the use of these newer methods of pelvimetry, it is apparent that we are in a process of transition from the general use of certain old-time methods to the adoption of newer and more accurate ones. These later methods have not only given us new concepts with regard to what we formerly considered the normal female pelvis but also a newer knowledge of the adaptation of the fetus to the birth canal in the process of birth. However, in any discussion of the usefulness of these methods we must not forget that the scientific conduct of labor involves so many factors that even possessing such exact dimensional knowledge, we should not form a concept of the process of birth which is entirely mechanical.

Let us consider for a moment some of these factors. The birth canal is composed not only of the bony structures but of soft parts, and the fetus also is composed in the same way. Mensuration of these bony structures therefore is not an entirely complete survey of the birth passage and its passenger. The forces which are concerned in labor are subject to influences which render them both voluntary and involuntary, and it would appear that much of this influence is hormonal in character. In addition, the influence of such factors as race, constitution, disease, emotion, and pain all share in the complex process. The usefulness of the knowledge of the dimensions of bony structures of the pelvis and fetus, therefore, has certain limitations, and to draw definite conclusions as to the outcome of labor without considering the whole picture is not only hazardous but unscientific. In other words, the greatly useful knowledge which these roentgen methods has given us must be properly assimilated with our greatest therapeutic weapon, namely, clinical experience. It is not enough to visualize the pelvis and fetus in space by means of roentgenograms. Indeed it is easy for the

2 cm. high and measured about 2 cm. at the base. A round pedicle about 8 mm. in diameter connected this portion with the aforementioned one. A fistula opened at the tip; it could be probed deep into the specimen. On microscopic examination the opening at the conical end corresponded to the interstitial portion of the tube. The mucosa was slightly inflamed but otherwise nothing unusual was seen. There were no glandular structures in the muscle tissue surrounding the interstitial portion of the tube. The myometrium was not inflamed. The large section of the muscle and fascial portion of the specimen showed very little change in the muscle tissue. Many tissue spaces in the fascia were distended and were lined with large cells, mostly of the character of foreign body giant cells. In some of the tissue spaces this lining was so regular that it simulated epithelium (Fig. 2). There were no epithelial structures. In the surroundings of this foreign body reaction, recent hemorrhage was found and much old blood pigment. There was much diffuse inflammation and some evidence of regeneration. A similar picture was seen in the smaller piece of tissue which consisted of muscle tissue and fat tissue with many lymphoid foci.

Diagnosis: Blood pigment and foreign body inflammation leading from interstitial portion of tube to the entis of the abdomen.

The points of interest in this case may be briefly summarized:

1. The fistula developed soon after a laparotomy where no drainage was instituted and no unabsorbable suture material used. Infection may be presumed to have been present. The production of the sinus tract probably followed the resolution of a hematoma or exudate around the stump of the left tube which became adherent to the lower angle of the incision, eventually breaking through the line of least resistance and leaving in its wake an irregular fistulous tract.

2. It was possible to demonstrate the tubo-abdominal fistula by means of a radiopaque substance which identified the tube involved, thus facilitating the operative procedure.

3. Though the fistulous tract could be probed, the pathologic examination failed to reveal any definite epithelialized tract. The microscopic section showed tissue spaces lined by foreign body giant cells, simulating epithelial-lined tracts. These spaces evidently provided the avenue of escape for the blood from the uterine cavity to the abdominal surface.

I want to thank Dr. Rubin for the privilege of reporting this case.

1000 PARK AVENUE

measured and delivered upward of 500 primiparous women. In conclusion, I would say that at the present time we have methods which are entirely adequate for measuring the pelvis as a routine procedure. Our next problem is to enrich our knowledge and experience by applying these methods to wide clinical use.

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VOLUMINOUS HERNIA OF THE CULDESAC OF DOUGLAS TREATED BY TOTAL COLPECTOMY

LOUIS E. PHANEUF, M.D., Sc.D. (HON.), F.A.C.S., BOSTON, MASS.

DURING the last twenty-one years I have encountered thirty-eight large hernias of the culdesac of Douglas. The terms posterior vaginal hernia and enterocele have also been applied to this lesion. While a small amount of bulging of the culdesac is usually associated with all extensive rectoceles, the large definite hernias are not commonly met. In my experience the vaginal operation devised by George Gray Ward, which consists of a free dissection of the sac from all its attachments, transfixion and ligature of the base after reducing its contents, resection of the sac, approximation of the uterosacral ligaments in the median line and a high perincor-rhaphy, is attended with very satisfactory results. For the hernias complicated by adhesions, I have resorted to the Moschcowitz operation, by obliterating the culdesac intraabdominally by means of superimposed layers of purse-string sutures. While this procedure was devised for prolapse of the rectum, it is equally efficient in the treatment of a culdesac hernia. My statistics show that twenty-eight patients were treated by the Ward technic and ten patients by the Moschcowitz procedure. Recently I have treated an enormous posterior vaginal hernia, the size of a fetal head, which could not be kept within the pelvis, even with the patient flat in bed. A small uterus was totally prolapsed and rested on the superior surface of the mass. Because of the large size of this hernia, I have employed total colpectomy or colpocleisis, with a gratifying result. The case of this patient forms the basis of the report which follows.

CASE REPORT

Mrs. C. McD., aged fifty-nine years, was admitted to the Gynecological and Obstetrical Service of the Carney Hospital on Aug. 26, 1936. She stated that five years ago she had first noticed a mass protruding through the vulva which she felt was "falling of the womb" and that the mass had become progressively more pronounced. There was nothing remarkable in her family and personal histories. The onset of menstruation occurred when she was sixteen years of age; the periods were of the twenty-eight-day type, lasted three days, and were painless. She had been married forty years, her husband having died of pneumonia, twenty years previously. She had had five children, all of whom were living and well, the oldest being thirty-eight and the youngest twenty-eight years of age. The first and third children were delivered instrumentally and the others normally. There were no abortions or miscarriages. She had occasional nocturia, getting up once at night, and she had always been obese.

inexperienced and enthusiastic to be sidetracked into false security if too much emphasis is given to roentgen information so obtained.

Roentgen methods are of great value, but they must be properly interpreted. At the present time, I have reached certain conclusions as to what should constitute an accurate and useful survey of the pelvis for practical obstetric purposes, and these are:

First: A roentgenogram showing the outline of the superior strait which may admit of reduction to its actual size and thus, drawn on centimeter paper, incorporated with the prenatal history. This procedure is entirely satisfactory in using the grid method plus the centimeter glass screen for reduction, the details of which I have set down elsewhere.¹

Second: A lateral pelvic roentgenogram which may also be plotted in the same manner as above if desired. This should depict all of the anteroposterior diameters from the superior to the inferior strait, the contour and position of the sacrum, and the character of the sacrosciatic notch. Lateral roentgenograms at term or early in labor have an added advantage in showing the size and station of the fetal head and the relationship of this body to the birth canal.

Third: By internal pelvimetry determining the bispinous diameter using the method described by Hansen,² and by external pelvimetry of the outlet determining the anterior sagittal, posterior sagittal and intertuberal diameters.

The above roentgen information may be obtained, using but two 10 by 12 inch films, thus reducing the cost to a practical minimum. I have previously emphasized the advantages of the routine use of measures similar to the above, and in primiparous women I am convinced that they are of paramount importance. The older methods of estimating pelvic capacity are unreliable even in experienced hands, and the loss of a baby through an untimely operative procedure or of a mother through a delayed cesarean section may occur in these same hands as a result of inexact knowledge of the pelvic capacity.

The routine use of these measures is bound to have influence on future obstetric procedure through the important knowledge that we have already obtained regarding variations of the pelvis. The occurrence of wide variations in pelvic form in presumably normal individuals has changed our whole concept of the "normal female" pelvis. The value of greater statistical and clinical knowledge of these variations in relation to labor is obvious if we consider what a large experience will offer. These measures become then of great importance to the individual and to the development of our knowledge of the subject.

The value of the routine use of the above procedures has become much impressed upon me during the past two years, in which time we have

Scott's solution. The uterine cavity measured two and one-half inches. A circular incision was made around the cervix and another around the prolapsed mass about 2.5 cm. below the urinary meatus. Vertical anterior and posterior incisions were made in the median line, uniting the two circular incisions. The vagina was then dissected off in two halves. The cervix was split in two, the anterior lip excised, then the posterior lip. The remaining cervical lips were approximated with five interrupted sutures of No. 2 chromic catgut, two on each side of the uterine cavity and one in the center over the canal, in which was tied a strip of Penrose tubing. The bladder and culdesac of Douglas were sutured to each other by means of interrupted sutures of No. 1 chromic catgut, gradually reducing the mass. Two purse-string sutures, one of No. 0 and one of No. 1 chromic catgut, superimposed, were placed in the perirectal fascia to reduce the rectocele. The edges of the vaginal incision were united with interrupted sutures of No. 2 chromic catgut, allowing the drain to come out through the central opening. The large mass was well reduced by this procedure.



Fig. 2.—Eighteen days after total colectomy, colpocleisis, and perineorrhaphy. The photograph was taken while the patient strained.

The pelvic floor was opened below the mucocutaneous border. The levator ani muscles were freed on each side and a flap of posterior vaginal wall dissected upward. The levator ani muscles and their fascia were approximated with four interrupted sutures of No. 2 chromic catgut, the triangular ligament was united with four interrupted sutures of No. 0 chromic catgut, as were the superficial perineal tissues. The vagina and external perineum were closed with interrupted sutures of No. 1 chromic catgut. The primary result appeared to be excellent. A self-retaining catheter was introduced into the bladder, about 1,000 c.c. of clear urine being obtained. The spinal anesthesia had been satisfactory and the patient was returned to bed in good condition.

The patient made a good recovery from anesthesia, being kept comfortable with small doses of morphine. She passed considerable urine through an indwelling catheter. Her bowels were closed for seven days. On the second postoperative day her blood pressure dropped to 110 systolic and 55 diastolic, for which 2 gr. (0.120 gm.) of thyroid extract, three times a day, were prescribed. Urinary antiseptics in the form of methenamine, acid sodium phosphate and ammonium chloride were

The physical examination revealed the blood pressure to be 212 systolic and 110 diastolic. Except for obesity there was nothing remarkable about her development. The head and neck were normal except for the fact that she had poor teeth. The chest was large and symmetrical; the lungs were normal; the heart was large, the aortic second sound being very sharp, and there were extra systoles and compensatory pauses. The abdominal examination showed diastasis of the recti muscles, a small umbilical hernia, marked obesity of the abdominal walls, and a pendulous abdomen. A hallux valgus was present on each foot, otherwise the extremities were not remarkable. Examination of the genitals revealed a mass the size of a fetal head which was extruded through the vulva and severely ulcerated. It consisted of a voluminous hernia of the culdesac of Douglas, on which rested a small atrophied uterus, in complete prolapse (Fig. 1). This mass, which rested on the bed between the patient's legs, was reduced into the pelvis, but it was impossible to keep it there, as it again rolled out with the slightest intraabdominal pressure. A consultation was held with



Fig. 1.—Hernia of the culdesac of Douglas, posterior vaginal hernia, accompanied by the total prolapse of an atrophied uterus. The dark spot in the center is the external os of the cervix.

the Medical Service of the Hospital, which advised slow digitalization because of her cardiac disorder and gave the preference to spinal anesthesia. The urine, which was acid, varied in specific gravity from 1002 to 1020, albumin varied from the slightest possible trace to a slight trace, and the sediment showed pus, free and clumped, and bacteria. The hemoglobin was 85 per cent, the red cell count 3,450,000, and the white cell count 8,900.

The patient was kept in bed from August 26 to September 8, during which time the ulcers on the prolapsed mass were painted with 4 per cent mercurochrome solution. On the last mentioned date the ulcers were completely healed and the blood pressure had dropped to 170 systolic and 90 diastolic. She was, therefore, prepared for operation, which was performed on Sept. 9, 1936.

Operation.—Spinal anesthesia was administered, using 200 mg. of novocaine crystals. The parts were scrubbed with green soap and water and painted with

Rosenthal^s reports a case of purpura appearing in a man after the ingestion of quinine. In an interval between attacks, the patient's idiosyncrasy to the drug was tested by the intradermal injection of a minute amount of quinine and urea hydrochloride. A profuse generalized purpura developed. The examination of the blood showed: "Hemoglobin, 90 per cent; red blood cells, 5,000,000; white blood cells, 16,000; platelets, 90,000; polymorphonuclear neutrophils, 50 per cent; lymphocytes, 42 per cent; monocytes, 6 per cent; coagulation time, nine minutes; bleeding time, three minutes; tourniquet test, positive; clot retraction, none."

CASE REPORT

Mrs. E. L. (Bronx Hospital No. 53603, Clinic No. 33199), a twenty-eight-year-old white woman, was admitted to the Obstetric Service of the Bronx Hospital at 3:45 P.M. on March 8, 1935, because of indefinite pains the day before, slight staining, and postmaturity. The expected date of confinement was Feb. 25, 1935.

The patient's general condition on admission was good. The blood pressure was 134/86; temperature, 98° F.; pulse, 80; respiration, 20; heart rate, 90. There was a systolic blow at the apex. The presentation was vertex R.O.A.; height of fundus, 40 cm.; fetal heart, R.L.Q., 132; fetal head engaged; dilatation of cervix, one finger.

A soapsuds enema was given at 4:10 P.M.; and labor was induced medically by means of two ounces of castor oil and 20 gr. of quinine administered in divided doses of 5 gr. at fifteen-minute intervals between 5:00 and 6:00 P.M. By 9:00 P.M. the pains had become regular and strong, and the patient was removed to the delivery room. The membranes ruptured spontaneously at 9:25 P.M., and ten minutes later the patient was delivered of a living female child weighing 9 pounds, 11 ounces. No anesthetic was required. Following the expression of the placenta, a first degree laceration of the perineum was repaired, and 1 c.c. of pituitrin was administered. The patient was returned to the ward one hour later.

The patient had attended the Antepartum Clinic since Oct. 2, 1934. Her previous medical, surgical, and obstetric history was negative. Menstruation occurred irregularly every sixty to ninety days; the last period was May 18, 1934. Wassermann and Kahn tests were negative, and the pelvic measurements were normal. The prenatal course was uneventful. The patient's first pregnancy had terminated in a normal child on Nov. 13, 1927.

At 11:45 P.M., March 8, 1935, two hours after delivery, the patient was found in severe circulatory collapse. Her blood pressure was 76/60; pulse, 100. She was very pale and was perspiring profusely. She had been bleeding moderately from the vagina since delivery. She was also bleeding from the gums, and there was a purpuric hemorrhage in the umbilical region. The vulva was edematous, and the vagina markedly ecchymosed. The patient now stated that six years prior to admission she had taken an emmenagogue, following which she had developed purpura and vaginal hemorrhage. Treatment had consisted of calcium and horse serum intramuscularly. Blood examination at that time had showed marked reduction of the platelets and prolonged bleeding time. After the patient's recovery, she had been given a teaspoonful of elixir of iron, quinine, and strychnine, following which purpura again developed; she was advised to take no more quinine.

A consultant then advised against retesting the patient for sensitivity to quinine, especially since her condition was poor, for his previous experience had shown the dangers of such a procedure. Morphine sulphate 0.25 gr., caffeine 7.5 gr., fluidextract of ergot 2 drams, and ernutin 1 c.c. were administered. The vagina was packed with iodoform gauze, through which the blood continued to ooze until March 12, when the packing was removed.

given while the self-retaining catheter was in place, and the perineal sutures were painted daily with 4 per cent solution of mercurochrome. The catheter came out on the seventh postoperative day and was not replaced. The drain fell out on the ninth day. She was allowed to sit in a chair on the sixteenth postoperative day and was discharged from the hospital on the eighteenth day after operation.

At the time of discharge the perineum was healed and gave good support. The vagina was healed. There was no bulging on hard straining. The result was satisfactory (Fig. 2). The patient was discharged cured.

In my experience of 38 posterior vaginal hernias, this was the largest encountered, and it was felt that it could not be cured by ordinary means.

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NOTE: The illustrated technic of total colectomy will be found in the AM. J. OBST. & GYNEC. 30: 548, 1935.

270 COMMONWEALTH AVENUE

PURPURA HEMORRHAGICA COMPLICATING THE PUERPERIUM*

A. CHARLES POSNER, M.D., F.A.C.S., NEW YORK, N. Y.

(From the Obstetric Service of the Bronx Hospital)

PURPURA, whether primary (essential) or secondary (either toxic or allergic) in nature, is a rare complication of pregnancy and the puerperium. In 1925 Rushmore¹ collected forty-seven instances from the literature, to which he added one case of his own. Several cases have been reported since then, bringing the total to about seventy. The mortality, as computed by deSaussure and Townsend,² is 55.7 per cent. Cases in which both mother and child are affected are unusual (seven in Rushmore's series), and recovery of both is exceptional.

Waltner,³ in 1924, reported a case, not cited by Rushmore, of a woman of thirty-eight years, who had displayed symptoms of essential purpura hemorrhagica intermittently since the age of fifteen. One pregnancy had been uneventful. In the seventh month of her second pregnancy, purpura again appeared. The child was born with purpura. Both patients recovered.

Liebling⁴ (1926) reported a case of purpura hemorrhagica, with recovery, in a mother and her newborn infant. The etiology was presumably a latent toxemia of pregnancy.

Rodcort's⁵ case of purpura in a newborn baby was attributed either to toxemia of the mother or to strangulation by the umbilical cord. The mother displayed thrombopenia but no purpura.

The cause of Siegler's⁶ case of purpura hemorrhagica was latent toxemia of pregnancy. Although the mother recovered, the child died at the age of four days, probably from purpura hemorrhagica; autopsy was not permitted.

Peshkin and Miller⁷ describe a case of allergic purpura hemorrhagica due to quinine and ergot taken as an abortifacient. Therapeutic abortion was performed, and recovery ensued.

*Read before the Section of Obstetrics and Gynecology, New York Academy of Medicine, January 28, 1936.

pulse rate, which was 160 on March 9, the day after delivery, subsided gradually until it reached 72 on the day of discharge. The blood pressure ranged between 150/90 and 70/50. Mother and baby were discharged on March 29, in good condition.

The baby developed a generalized purpura shortly after birth. Purpuric and ecchymotic spots appeared on the abdomen, chest, both forearms, and thighs. Twenty c.c. of whole blood were administered intramuscularly the day after birth. A slight subconjunctival hemorrhage was noticed on March 11; the fundi were normal the following day, however. A quinine patch test, made March 15, was negative. The purpuric spots had practically disappeared at the time of discharge.

At postpartum examination on April 13, 1935, the condition of both patients was good, and purpura was no longer present.

During convalescence, the mother admitted having been confined in Rockland State Hospital for "nervous breakdown." Her record from that institution shows that she was admitted on Dec. 29, 1933, with dementia precox, catatonic type. She was discharged as improved on March 17, 1934. During the night of Feb. 14, 1934, the patient's nose began to bleed, and continued to bleed until the following day. There was also hemorrhage from the gums, and purpuric spots were present on the bridge of the nose, buccal mucous membranes, and inner surfaces of the thighs. The diagnosis was purpura hemorrhagica.

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1132 PARK AVENUE

Bacon, H. E.: The Specificity of the Frei Test in Lymphopathia Venera, Am. J. Digest. Dis. & Nutrition 2: 570, 1936.

The author presents an extensive review of the literature and emphasizes the importance and specificity of the Frei test in lymphopathia venera or lymphogranuloma inguinale. He stresses the importance of proctologic examination. In a series of 155 cases 96.7 per cent gave a positive Frei test. Three of the remaining 5 patients showed a positive Wassermann reaction. During the institution of antisyphilitic therapy and even after the completion of the course, he repeatedly failed to obtain a positive Frei test. Bacon feels that apparently there exists a reciprocal immunologic reaction between syphilis and lymphopathia venera. He calls attention to other authors who noted that in the presence of a recent or an active syphilitic process the Frei test may be rendered temporarily inactive.

His observations over a period of two years on the Frei reactions in various stages of the disease indicate that in the presence of clinical evidence one negative test does not exclude presence of this disease.

J. P. GREENHILL.

At 2:00 A.M., March 9, the patient received 600 c.c. of whole blood by the Soresi method; at 5:10 A.M., 500 c.c.; and at 3:30 P.M., 500 c.c. As hemorrhage from the vagina and gingival margins persisted, the patient was given another transfusion of 500 c.c. on March 10. The fifth and last transfusion, of 400 c.c., bringing the total to 2,500 c.c., was administered on March 13.

On March 11, numerous purpuric spots were observed on the left forearm. Marked ecchymosis was present at the site of transfusion. The mucous membranes were pale. Eye examination showed subconjunctival hemorrhage and pallor of discs.

TABLE I. BLOOD OF MOTHER

DATE	H.B.	R.B.C.	W.B.C.	POLYS	BAND	LYMPH.	MONO.	PLATELETS	BL. TIME	COAG. TIME
3/ 9/35*	65%	3,600,000	35,300	76%	12%	4%	8%	17,000	45+ min.	2½ min.
3/10/35†	40%	2,650,000						21,000		
3/11/35	45%	1,680,000	19,800	86%		6%	7%	40,000	3 min.	5 min.
3/12/35	37%	1,800,000	14,000	74%	11%	12%	3%	128,000	2½ min.	4 min.
3/13/35‡	45%	2,670,000	15,200	76%	10%	7%	7%	120,000	3 min.	4 min.
3/15/35	52%	2,880,000	18,400	64%	7%	17%		144,000	2 min.	7 min.
3/16/35	49%	2,490,000	18,700	70%	6%	13%	11%	230,000	4 min.	3 min.
3/18/35	46%	2,520,000	10,400	73%	1%	24%	2%	184,000	2 min.	4 min.
3/19/35	50%	2,900,000	10,800	67%	2%	30%	1%	210,000	3 min.	4½ min.
3/20/35	58%	2,880,000	9,200	64%	4%	26%	6%	208,000	1 min.	2 min.
3/21/35	58%	3,240,000	11,400	73%	2%	17%	8%	216,000	1 min.	2½ min.
3/22/35	52%	3,420,000	9,700	60%		32%	6%	228,000	1 min.	2 min.
3/23/35	57%	3,410,000	11,500	61%	2%	33%	4%	230,000	2 min.	5 min.
3/25/35	58%	3,120,000	11,200	61%	3%	24%	12%	226,000	1 min.	2 min.
3/26/35	52%	3,800,000	9,000	71%	2%	22%	5%			
3/28/35	68%	3,790,000	7,900	54%		44%	2%	288,000	1 min.	3 min.
3/29/35	74%	3,800,000	6,100	73%	2%	23%	2%	230,000	2 min.	3 min.

*1600 c.c. whole blood administered by three transfusions.

†500 c.c. whole blood administered.

‡400 c.c. whole blood administered.

TABLE II. BLOOD OF BABY

DATE	H.B.	R.B.C.	W.B.C.	POLYS	BAND	LYMPH.	MONO.	PLATELETS	BL. TIME	COAG. TIME
3/ 9/35	60%	2,980,000	24,500	39%	8%	48%	5%	10,000	25+ min.	1½ min.
3/11/35	47%	3,280,000	14,000	54%	12%	17%	10%	24,000	5 min.	3 min.
3/12/35	64%	2,800,000	14,200	74%	5%	10%	2%	36,000	3 min.	4 min.
3/13/36	64%	4,230,000	10,000	57%	10%	26%	7%	55,000	3 min.	3 min.
3/14/35	65%	2,620,000	11,400	50%	4%	34%	2%	88,000	2 min.	4 min.
3/15/35	63%	3,760,000	10,900	50%	6%	34%	8%	96,000	2 min.	3 min.
3/18/35	78%	4,200,000	10,300	10%	6%	80%	4%		3 min.	3½ min.
3/25/35	65%	4,080,000	14,000	36%		53%	11%	220,000	1 min.	2 min.

The decrease of the purpuric spots began on March 17. Frequent examinations of the blood of both mother and baby were made, as shown in Tables I and II. Examination of the feces of both mother and baby revealed no occult blood; the benzidine tests of both were negative.

The mother's condition improved gradually. Iron and ammonium citrate and liver extract were administered daily. The temperature fluctuated between 99.8° F. and 103° F. until the twenty-first day of illness, when it returned to normal. The

and its consistency soft and crumbly. The myometrium had partially been replaced by this tumor tissue, but a distinct line of demarcation could still be made out. Normal endometrium could not be recognized throughout the entire mucous membrane, the tumor extending continuously to the point of amputation.

Microscopic.—Histologically, the endometrium was seen to be replaced by a tissue composed of squamous cells arranged in the form of compact papillary cords tending to form rounded or clubbed ends. This tissue extended down to the myometrium where a distinct line of demarcation could be distinguished. The squamous cells composing the tumor tissue were immature, in the main being in a transitional stage.



Fig. 1.—Gross specimen. The entire endometrium is replaced by a papillary tissue which measures 0.5 cm. in diameter.



Fig. 2.—Very low power. The papillary structures in the form of dense compact masses are distinguishable. In the lower left corner slight infiltration of the myometrium can be seen.

In areas, beginning keratohyalinization could be seen, and here occasional mature cells showing mitotic figures were discernible. Arrangement in the form of "pavement" stratification was also present. Numerous sections taken through different areas of the uterine wall failed to show even the slightest evidence of normal endometrium.

Following the operation the patient's recovery was uneventful, and after three weeks she was transferred back to the Morrisania Hospital for the purpose of receiving more radiotherapy. She has been there ever since, and has received 8,000

DIFFUSE SQUAMOUS CELL CARCINOMA OF THE UTERUS

FRANK SPIELMAN, M.D., NEW YORK, N. Y.

(From the Gynecological and Obstetrical Service and Department of Laboratories of the Lincoln Hospital)

DIFFUSE squamous cell carcinoma involving the fundus of the uterus was first described by Ruge¹ in 1882. Since that time approximately 40 cases have been reported in the literature. The condition probably occurs with much more frequency than is suspected, and its nonrecognition must be attributed to the fact that radiotherapy has become almost universally the method of treatment in carcinoma of the cervix. Since the acceptance of this form of treatment makes the opportunities for the study of such material as is here presented more and more limited, the following case is worthy of detailed recording.

REPORT OF CASE

A. M., aged sixty-five, never gravid, was admitted to the Lincoln Hospital on Sept. 22, 1934, complaining of vaginal bleeding of eighteen months' duration. She had menstruated regularly until her menopause at the age of forty. In October, 1933, she had been at the Morrisania Hospital where an epidermoid carcinoma of the cervix was found, for which she received 3,060 mg. hr. intrauterine radium, and 5,040 mg. hr. to the cervix. Following this she was free of bleeding until one month before admission to the Lincoln Hospital, at which time she was again bleeding profusely. Her general physical and laboratory examinations were essentially negative. Pelvic examination showed a shortened, contracted vagina which admitted only one finger to a depth of one inch. There were senile changes and desquamation of the vagina, so that the cervix could not be felt.

All parametria were obliterated. On rectal examination a short cervix, and a retroverted soft uterus enlarged to the size of a two months' gravidity could be palpated. Because of the enlarged soft uterus, and because the patient had received radiotherapy to the cervix, it was felt that the body of the uterus rather than the cervix was the cause of the bleeding, and a hysterectomy was decided upon. A supravaginal hysterectomy with bilateral salpingo-oophorectomy was performed under general anesthesia with comparatively little difficulty, care, however, being exercised to wall off the uterine cavity at the site of amputation by means of large clamps in order to prevent soiling of the peritoneum by any material present in the uterus.

PATHOLOGIC REPORT

Gross.—The specimen consisted of a symmetrical uterus which had been supravaginally amputated, enlarged to the size of a two-and-one-half-month gravidity. Its external surface was smooth, peritoneal surface intact, and consistency cystic. On section, the uterine cavity was distended due to the presence of about 3 ounces of seropurulent exudate. The endometrium in its entire extent was replaced by a friable papillary tissue having a thickness of 0.5 cm. Its color was grayish white

2. Those primary in the fundus with spread downward.

3. Those in which no primary lesion can be recognized, the carcinoma appearing as one continuous tumor lining the endometrium symmetrically.

According to this classification, the case here reported in all probability falls within the first group, for, although absolute proof cannot be advanced because the cervix was never removed, the very first examination at the Morrisania Hospital showed a lesion sufficiently large to warrant its acceptance as being primary.

Diffuse carcinoma involving not only the body and the cervix but also the vagina has been recorded only twice, a case by Schauenstein⁴ and one by Gellhorn.⁵ The above case which shows definite involvement of the vagina without infiltration of the parametria must be considered as the third case on record.

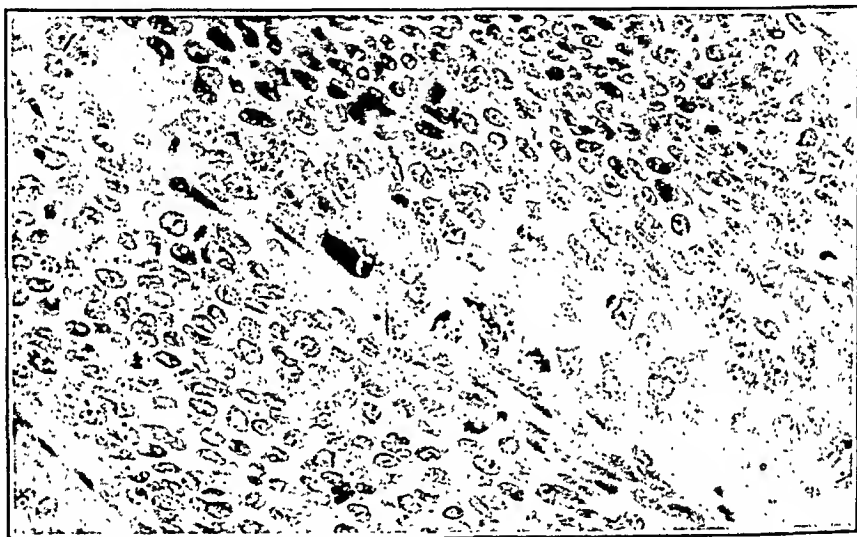


Fig. 5.—High power. Keratohyalinization is seen as well as numerous mitotic figures.

R. Meyer⁶ believes that the spread of the carcinoma occurs along the surface of the normal endometrium with secondary penetration toward the base. Cases in which areas of squamous cells have penetrated into the glands and then deeply into the endometrium have been observed to support this contention. The case under discussion fails to show even the faintest evidence of the presence of normal endometrium so that the method of spread of the carcinoma cannot be determined. The complete replacement of the endometrium by the carcinoma is in itself of interest.

That a metaplasia of the endometrium may have occurred must be considered. As R. Meyer⁶ has pointed out, infection undoubtedly plays a rôle in the change to squamous cells. Almost every case reported has occurred in women in the senium and has been accompanied by a pyometra. This is also true of the case reported here. In addition, treatment with intrauterine radium may also have been an influence.

R.U. to the pelvis, as well as about 1,500 mg. hr. of radium to the vagina and recto-vaginal septum. Recent examination shows ulceration and infiltration of the vagina and the rectovaginal septum. There is no parametrial involvement, nor are any adnexal masses palpable. Biopsy taken on May 15, 1935, from the vaginal infiltration shows an acute inflammatory exudate, single groups of squamous hyperchromatic cells, and giant cells.



Fig. 3.—Low power. The nature of the papillations is shown. They are composed chiefly of transitional squamous cells, immature in type.

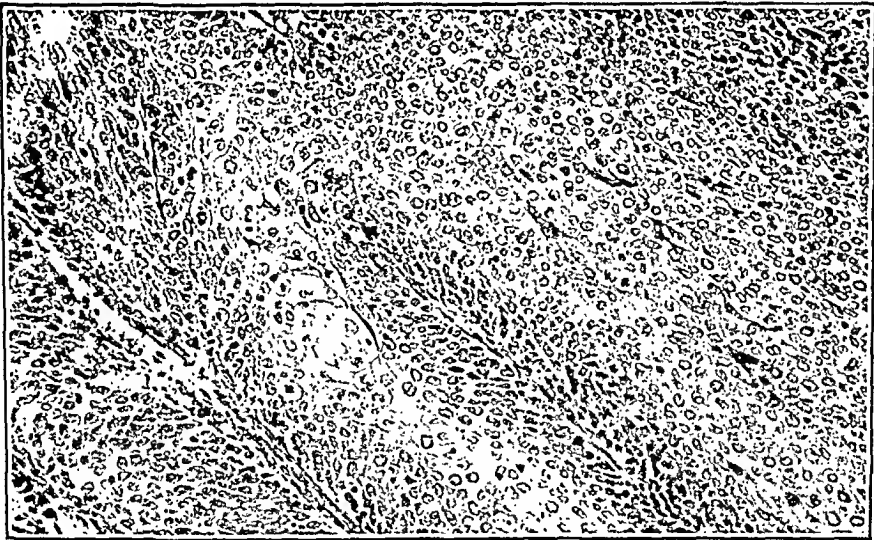


Fig. 4.—Higher power. The transitional cells are distinguishable and there is a tendency toward the formation of the adult type of epithelium. The arrangement is of the "pavement" type. There is also evidence in the center of keratohyalinization.

DISCUSSION

Squamous cell carcinoma of the body of the uterus has given rise to considerable discussion. Lahm^{2, 3} has collected 20 cases from the literature and has divided them into three groups according to the origin:

1. Those arising from a primary carcinoma of the cervix with spread upward by continuity.

There were no other pertinent facts in her history and her general physical examination was negative. She had an appendectomy in 1927, and was operated upon again in 1928 for adhesions.

Pelvic examination showed good perineal support, cervix eroded on posterior lip, body of uterus forward, soft, regular in outline, size of a three months' pregnancy,

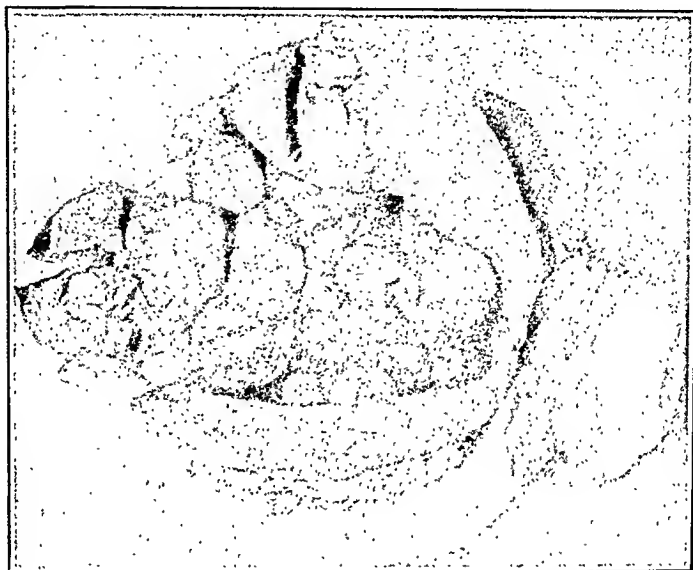


Fig. 1.—Uterus and mole, actual size. Embryo is 14 mm. long.

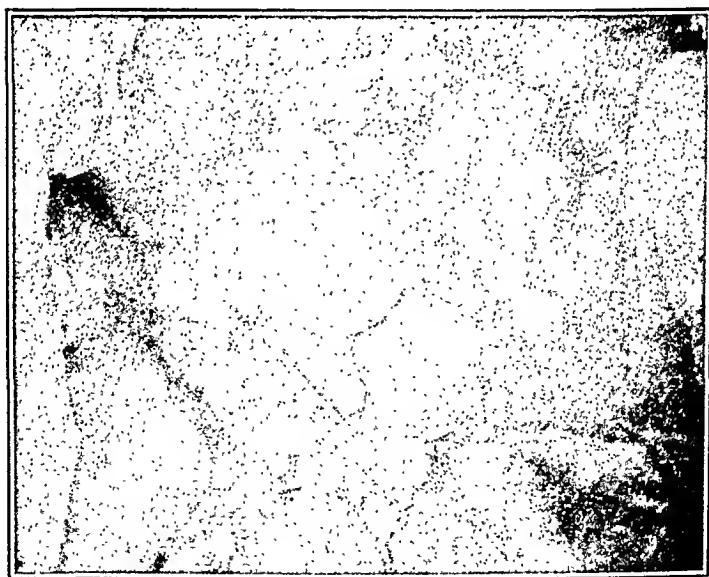


Fig. 2.—Embryo, cord, and placental tissue, 3 \times normal size.

adnexal regions and culdesac negative. A Friedman pregnancy test was done and the report was negative. Diagnosis: Probably soft fibroid.

Operation on March 11, 1936, midline incision revealed a soft uterus size of a three months' pregnancy. A complete hysterectomy was performed and the correct diagnosis was not made until the uterus was cut open. There was a gush of chocolate-colored amniotic fluid, the interior of the uterus filled with a blood mole presenting a polypoid appearance (Fig. 1). Later a small fetus measuring 14 mm. was ob-

As has been stated, treatment of carcinoma of the cervix by radiotherapy has merited universal adoption. However, the possibility of spread to the fundus with the formation of a pyometra brings up the question of further therapy. Where the pyometra is recognized, treatment of this condition alone is indicated. Where spread of the carcinoma to the fundus and even through it, as has been reported,⁷ has taken place, the advisability of removal of the uterus surgically must be entertained.

SUMMARY AND CONCLUSIONS

1. A case of diffuse carcinoma of the uterus accompanied by pyometra, for which hysterectomy was performed, is presented.
2. Its origin was probably in the cervix with extension upward to the fundus as well as downward to the vagina, leaving the parametria uninvolved.
3. The possibility of the occurrence of spread to the fundus from a primary carcinoma of the cervix with pyometra formation must be considered and here the question of hysterectomy must be entertained.

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145 WEST EIGHTY-SIXTH STREET

MISSED ABORTION—A HEMATOMA MOLE

EARL C. SAGE, M.D., OMAHA, NEB.

MRS. H. O. (University Hospital No. 52859), aged twenty-five years, white, admitted March 3, 1936, dismissed March 22, 1936, on tenth postoperative day. Operation March 11, 1936, hysterectomy complete, spinal anesthesia; 17 mg. of pantocaine.

This patient entered the hospital because she knew she had a uterine tumor; because she had a period of amenorrhea from April, 1935, until December, 1935, and because she had irregular menstrual periods from December, 1935, to March, 1936. This latter flowing would occur every two to fourteen days.

Her last normal menstruation was then eleven months ago.

She was the mother of 2 children, aged four and two years, the last child was born in November, 1933. She started to flow six weeks later and had a normal menstrual cycle until April, 1935.

She consulted a doctor in June, 1935, who made the diagnosis of probable pregnancy. In October, 1935, four months later, she consulted her physician because her abdomen failed to enlarge. Her doctor told her he believed the fetus was dead and that at some future time she would deliver a dead fetus. Nothing happened so she waited until January, 1936, before she was examined again on account of irregular vaginal bleeding. She was referred to the University Hospital with the diagnosis of a soft fibroid.

ATELECTASIS AS A COMPLICATION OF OBSTETRIC ANALGESIA

GOODE R. CHEATHAM, M.D., ENDICOTT, N. Y.

(From the Obstetrical Department of the Endicott-Johnson Medical and Ideal Hospital)

AT THE present time obstetric analgesia is a much discussed subject among both the laity and the profession. The very multiplicity of methods and drugs used is prima facie evidence that the ideal combination has not yet been found, and it is not my purpose to enter into any lengthy debate as to the relative advantages or disadvantages of the various methods advocated, but to call attention to a rather serious disadvantage associated with an otherwise satisfactory form of obstetric analgesia, namely nembutal (pentobarbital sodium) and paraldehyde.

At various times we have used innumerable types of obstetric analgesia, including morphine and scopolamine, Gwathmey technic, McCormick modification of the Gwathmey technic, the barbiturates alone or in various combination and others. We found the combination of nembutal by mouth and paraldehyde in olive oil by rectum as advocated by Conn, Leighton, and Ross to be the most universally satisfactory in our hands, and it is today our routine procedure for uncomplicated cases. Having adopted this technic because of its almost universal amnesia, its simplicity of administration and its safety factor, it is with regrets that the following cases are very briefly summarized:

CASE 1.—K. K. (No. 22444), aged thirty years, para i, admitted to Ideal Hospital with ruptured membranes but no pains. Labor began at 1:00 p.m. August 20, and continued with good pains.

At 1:20 A.M., next day, analgesia was begun. Progress was satisfactory. At 10:00 A.M., respirations suddenly increased to 45, the patient became slightly cyanotic, pulse 110. A half hour later respirations were still labored, caput presenting. A normal live baby was delivered by low forceps.

The patient was given inhalations of carbon dioxide and oxygen, and injections of caffeine sodium benzoate were begun. A chest examination rather hurriedly done revealed diminished breath sounds at the lower left base with occasional coarse râles, and a tentative diagnosis of atelectasis of the left base was made. The patient was put in an oxygen tent, caffeine continued together with frequent changing of position. In a few hours the patient's respirations were 30, less labored and the cyanosis was gone. X-ray showed: "Slight haziness at base of left lung. Heart not retracted to left. Possible clearing atelectasis." The patient's convalescence was uneventful and she was discharged on the tenth day postpartum with a well baby.

CASE 2.—R. S. (No. 23009), aged thirty-three, para vi, admitted to Ideal Hospital Oct. 22, 1936, in labor. At 10:50 A.M., analgesia was begun and at 12:40 p.m., normal spontaneous delivery of a live baby occurred.

At 4:00 p.m., respirations increased rapidly to 40, pulse 120. Patient cyanotic. Axillary temperature (patient restless) 99° F. Chest examination revealed diminished breath sounds in right axilla, coarse râles over anterior chest to right of the sternum. Impression was atelectasis of right chest. X-ray was not taken. Patient was given carbon dioxide and oxygen inhalations, caffeine sodium benzoate and placed in an oxygen tent. Position frequently shifted. Her recovery was almost as rapid as onset. She was discharged on the tenth day postpartum with a well baby.

served in this mass of polypoid growths. This fetus was from five to seven weeks of age with a distinct umbilical cord, external indications of eyes, buds representing the extremities (Fig. 2).

Microscopic Findings: There were a number of sections taken from the uterine wall, including the placental tissue. There was no appreciable change in the muscularis. The endometrial glands were greatly distended and filled with a precipitate of albuminous fluid. Stroma cells were comparatively large and the stroma in some areas was quite edematous. Epithelial cells showed little change and only in a few areas was there definite decidual reaction. The placental tissue was largely necrotic but a number of villi near the endometrial surface showed fairly normal syncytial cells which stained very well. The stroma of some of these villi was quite normal in appearance. No blood vessels were seen within these villi. There was massive hemorrhage into the placental tissue. Much of the amniotic surface was necrotic, although in other areas a thin zone two or three cells deep remained viable (Fig. 3).

Diagnosis: Hematoma mole.



Fig. 3.—Section of the uterine wall, showing distended glands, and the border of the placental tissue, with a few viable villi.

As Taussig points out, the size of these embryos is fairly constant ranging from 8 to 15 mm. in body length. This definitely establishes the hematoma mole as a retained abortion from between the fourth and seventh weeks of gestation.

In cases associated with continued growth of the fetal membranes after embryonal death, there is a definite increase in the size of the cavity, and an early hydramnios, as was present in this case.

Usually the uterus will expell these products of conception, but in this instance there was only a little irregular uterine bleeding from December, 1935, although the patient's last menstrual period was April, 1935, eight months previously. There were no signs of cervical dilatation in March, 1936, eleven months after the last normal menstrual period. The Friedman test for pregnancy was negative. This test should be positive if there are any active live products of conception present in the uterus as would be obtained in an incomplete abortion, hydatidiform mole, or chorionepithelioma. This test is a placental sign and should be positive in the presence of active placental tissue.

A case of missed abortion varies in its duration from one or two months to one or two years. This case was a missed abortion of eleven months' duration.

A SATISFACTORY LEG SUPPORT FOR THE LITHOTOMY POSITION

JOHN B. PASTORE, M.D., NEW YORK, N. Y.

(From the Department of Obstetrics and Gynecology, Cornell University Medical College and the New York Hospital)

THERE has been considerable discussion as to the proper method of placing the patient in the lithotomy position for obstetric and gynecologic operations. More recently Thompson has shown that foot-drop following delivery is associated with pressure over the head of the fibula rather than with injury to the sacral plexus due to rotation of the fetal head in the pelvis. Such injury may be caused by most of the stirrups in general use today.

In obstetrics it is also desirable to permit mobility of the legs for two reasons: first, many of the patients are kept in this position for varying periods of time before the induction of anesthesia and the actual delivery, and second, in some of the obstetric procedures it is necessary to place the patient in the Waleher position

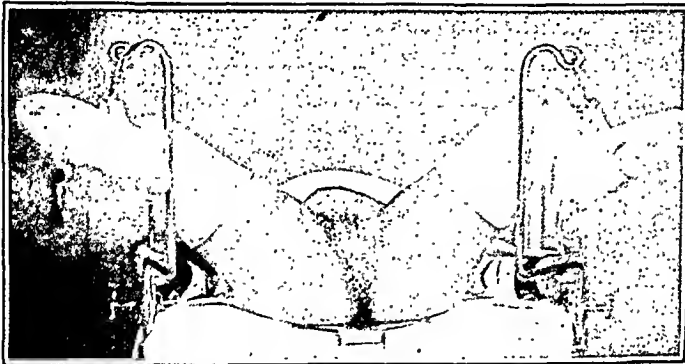


Fig. 1.—Patient in lithotomy position, using “beach slippers” to suspend the legs.

to facilitate delivery. For these reasons it is undesirable to have the legs fixed to a knee support. In our own experience we have found it unnecessary to employ two assistants to hold the legs in the proper position.

The method which we have used with satisfactory results for the past three years is shown in Figs. 1 and 2. The feet are suspended from the upright bars by means of straps attached to ordinary “beach slippers.” These slippers are inexpensive and are made of canvas so that they can be easily washed. The zipper permits easy manipulation and prevents the foot from slipping out of the stirrup during excitement. The straps are sewn to the sides of the slippers so that the pressure is distributed over the plantar surface of the foot. There is no circular pressure around the foot or the ankle as is obtained by other methods. When the patient “pushes” there is no direct contact of the leg with any metal portion of the stirrup, and therefore padding is not necessary. The upright bars are on the medial aspect of the legs. When the patient is anesthetized, the legs become abducted by their own weight and plantar flexion of the feet is impossible. There can be no pressure over the head of the fibula. The patient in Fig. 1 is not under the influence of anesthesia, so that complete abduction of the leg is not demonstrated.

CASE 3.—R. B. (No. 23116), aged twenty-nine, para i, admitted to Ideal Hospital Nov. 6, 1936. Contractions irregular, no dilatation. At 4:40 A.M., analgesia begun and at 8:00 nembutal, gr. iii, given additional. At 1:40 P.M. caput presenting with perineal bulging. Left lateral epistomy, and low forceps. Normal, live baby, patient's condition good. About an hour later respirations 32, pulse 120. No cyanosis, caffeine sodium benzoate given and position frequently changed. At 4:00 P.M., respirations 42, pulse 132, temperature 101.4°, cyanotic. Chest examination revealed diminished breath sounds over the lower right side of the chest with diminished expansion. Few coarse râles. Impression: Atelectasis or partial collapse. Carbon dioxide and oxygen given. Rapid digitalization begun and patient placed in an oxygen tent. A bedside x-ray was taken which showed, "slight irregular density mesial half lower right lung. Heart on right; maybe due to atelectasis."

Convalescence uneventful and the patient was discharged with a well baby on her tenth day postpartum.

These patients had nothing in common except the analgesia. They had no cold or cough on admission and labor was not unduly prolonged in any case. Naturally the question will be raised, "Were these cases of true atelectasis?" In only one case are we certain but the progress and clinical signs seem to justify the diagnosis. We have no way of proving the atelectasis due to the analgesia used. It might have occurred with the use of other drugs or general anesthesia, but on a fairly active service we have never had it occur with other forms of analgesia or general anesthetic. It could even have occurred without any analgesia or anesthetic for we have seen one case of spontaneous atelectasis occur in a seven months', otherwise normal pregnancy. The diagnosis in this case was confirmed by several internists and by x-ray. Granting that it could have occurred without any analgesia or anesthetic or with other analgesias or anesthetics, the short interval between the occurrence of three cases all having the same medication points strongly to the medication as the etiologic factor.

The mechanism of atelectasis (passive) in these cases is most probably due to a plugged bronchus. With the patient in a fairly deep stage of narcosis, it is easy to understand how mucus may be inspired, plug a bronchus and cause atelectasis or partial collapse.

A review of the recent literature reveals no reported cases of atelectasis occurring in conjunction with the use of obstetric analgesia. Whether these cases are isolated incidents or whether this is a not uncommon complication, I am not prepared to say at present. The ultimate outcome was highly satisfactory, but it is still a complication to be prevented if possible. There is nothing more disconcerting than to complete a labor, apparently satisfactorily, then receive a hurried call from the interne several hours later that the patient has suddenly "gone bad." Many glowing reports of the safety and advantages of various forms of analgesia are reported. It is equally important that all unsatisfactory results and complications be carefully noticed and reported lest we, in an earnest endeavor to alleviate the pain of labor, actually endanger the safety of the patient.

The administration of atropine sulphate gr. 1/150 when analgesia is effective is suggested as a prophylactic measure.

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In the series of 178 patients examined in the Gynecological Clinic 11, or 6.2 per cent, were found to have positive smears for gonorrhea. Of these 11 patients only 3 were infected with both the gonococcus and the parasites. Collis demonstrated the gonococcus in 20 per cent of 47 patients examined at the General Hospital, Birmingham. The frequency of the double infection convinced Collis that gonorrhea may reduce the resistance of the vaginal tract, making subsequent trichomonas infection more frequent.

The findings in this series would indicate that possibly the association with a gonorrheal infection is coincidental.

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A NEW TYPE OF SYRINGE ADAPTED FOR THE TREATMENT OF ENDOCERVICITIS

F. G. FALLON, M.D., AND MARION DOUGLASS, M.D., F.A.C.S.,
CLEVELAND, OHIO

(From the Department of Obstetrics and Gynecology of the Western Reserve University School of Medicine and the Lakeside Hospital)

THE treatment of chronic endocervicitis has been attended always with considerable difficulty. There is a distinct class of cases characterized by stubborn and persistent leucorrhea of various types but without marked laceration or erosion. Many of these cases, although the glands are deeply infected, do not show marked nabothian cyst formation grossly. The classical method of treating these cases usually has been the local application of drugs in the form of caustics, ordinarily some form of the silver compounds, antiseptic powders, or injection of various drugs into the cervix. Medicated pastes have been injected into the cervical canal. Various forms of cautery treatment have been effective usually in more severe cases with anatomic lesions, but particularly in specific cases of chronic endocervicitis, the gentle and judicious use of chemical agents is still the method of choice.

Application of liquids in the form of silver nitrate, mercurochrome, iodine, the anilin dyes, etc., is ineffectual often because the surface merely is treated, and the drug has slight chance of penetration and its germicidal power is necessarily limited. The application of a water soluble jelly of antiseptic nature would seem to be more rational. This can be delivered into the cervical canal, dammed or blocked at the external os by tampon of nonabsorbent cotton. The gradual liquefaction of a jelly allows more prolonged contact with the endocervix and improved chance for penetration. Water soluble jellies or ointments are readily prepared with gum tragacanth, glycerin, and water, using mercurochrome, iodine, potassium iodine, phenylmercury nitrate, merthiolate, etc. This, we have found to be the most convenient of all methods in the treatment of gonorrhea limited to the cervix, where extreme gentleness is absolutely necessary due to the danger of inciting an ascending infection.

The loading of the ordinary barrel type of syringe with ointment or jelly is inconvenient and difficult, and the instrument which we have to describe is a side-

For those who find it necessary to employ the Walcher position during part of the procedure, the swivel attachment of the upright bars is available on many of the operating tables. This permits the angle of the bars to be changed so that the legs can be lowered to any desired position.

In our own experience this method has been entirely satisfactory since we have had no cases of foot-drop or injury due to pressure on the legs or feet. It offers the following advantages:

1. The slippers are inexpensive, easily washed, and comfortable. (Sizes 8 and 9 are suitable for the average patient.)

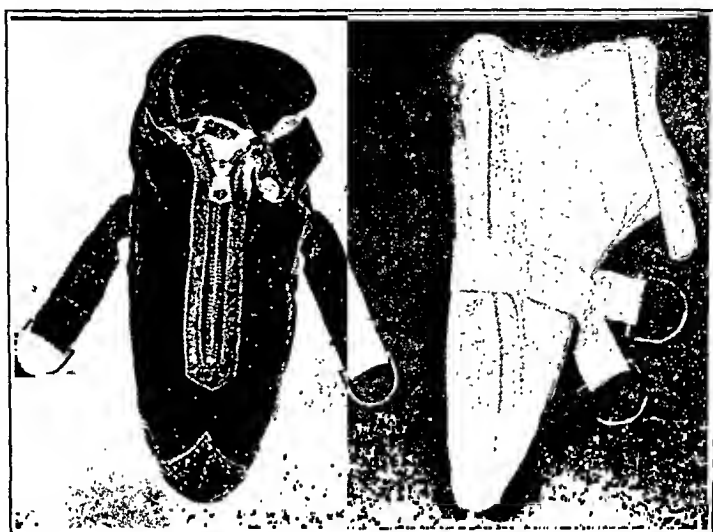


Fig. 2.—Photograph of slippers with straps attached.

2. Eliminates any external pressure over the legs and ankles.
3. Prevents plantar flexion of the feet.
4. Permits mobility of the legs while the patient is awake.
5. Permits the use of the Walcher position without difficulty.

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Thompson, J. E. M.: AM. J. OBST. & GYNEC. 29: 216, 1935.

THE INCIDENCE OF TRICHOMONAS VAGINALIS INFECTIONS

SAMUEL B. POTTER, M.D., DENVER, COLO.

(From the Department of Obstetrics and Gynecology of the University of Colorado School of Medicine)

AT THE University of Colorado School of Medicine and Hospitals a total of 325 nonselected white patients was personally examined for the trichomonads. Of these, 145 were pregnant patients at various stages in the Antenatal Clinic for routine care. The remainder, or 178 cases, were patients registering in the Gynecological Clinic. Of the total 325 cases, the parasite was found in 59, or 18.1 per cent. Of these 59, or approximately 30 per cent, complained of symptoms. In the series of 145 pregnant cases, 25, or 17 per cent, were found infected. Of these 25, or 24 per cent, complained of symptoms. In the nonpregnant series 34, or 19.1 per cent, presented the trichomonads. Of these 34, or 35.3 per cent, complained of symptoms.

Department of Book Reviews

CONDUCTED BY ROBERT T. FRANK, M.D., NEW YORK

Review of New Books

Obstetrics

Schumann has written *A Textbook of Obstetrics*¹ which is most carefully planned and well executed. Each word of the text appears to have been weighed. It is designed for students and practitioners, written by a man long engaged in the practice of the obstetric art, and based on a wide clinical experience. The pathology of each disease is taken up in detail, simply and clearly stated. Debatable and purely theoretical questions are considered but not emphasized. All well-authenticated methods of treatment are described. The writer then indicates his own preferences—for example the use of morphine and scopolamine for analgesia—after detailing all analgesics and anesthetics.

The introductory chapters on anatomy, physiology, fertilization and growth of the ovum are short, include all modern conceptions and are very well illustrated.

In normal labor the author suggests that the Credé maneuver be practiced 30 minutes after birth of the child if the placenta has not separated. If this is unsuccessful, the cord may be clamped and the placenta left in situ for 24 hours. With this we fully agree. But not with his next sentence in which he says, "It is better, however, to perform manual removal, after an interval of 2 hours, or if hemorrhage or any other indication arises." The general practitioner had better be counseled to keep his hands out of the uterus unless very vital indications develop. In abnormal conditions, Schumann is terse and to the point. "There is no expectant treatment for placenta previa." Naturally he modifies this for special circumstances. He prefers cesarean section in placenta previa unless the case is mild, as for example in multiparae well advanced in labor, where simple rupture of the membranes may suffice. In premature detachment of the placenta cesarean section is always advocated for an undilated cervix, and if the uterus is found soft, boggy, and containing hematomata, hysterectomy should complete the operation. The description of eclampsia is fortunately devoid of the innumerable and confusing theories and hypotheses which so often becloud the issue for the practitioner. The most conservative measures are advocated and only in the severest cases is labor induced in multiparae or those well advanced in labor, by means of rupture of the membranes. Rarely is cesarean section practiced for this indication.

The chapter on ectopic gestation is very ample and beautifully illustrated. For puerperal sepsis he believes that local treatment has little place in its management. The anomalies of the birth canal are very lucidly discussed. This volume concludes with a discussion of operative obstetrics. In forceps delivery, the Kielland forceps are stressed. Chapters on breech extraction, version, and cesarean section conclude the text. At the end of the volume is a short but carefully selected bibliography.

¹*A Textbook of Obstetrics.* By Edward A. Schumann, M.D., F. A. C. S., Professor of Obstetrics, School of Medicine, University of Pennsylvania, etc. 780 pages with 581 illustrations. W. B. Saunders Company, Philadelphia, 1936.

loading type of syringe with a large slot which fits perfectly into a slightly larger outside barrel, to the inside of which is soldered a cover for the slot of the inner barrel (Fig. 1). The composition plunger is forced through the inner barrel which allows little or no leakage of the jelly. This plunger is cup-shaped and may be of rubber or better of rubberoid composition. Pressure on the plunger (Fig. 1) expels the jelly through a tip six inches long and gauged to accommodate the curve of the cervical canal. These are in graduated sizes and are adapted to any type of cervical canal. Injection with this method is easy, harmless to the patient, as the treatment is accomplished carefully and under very low pressure, only suf-

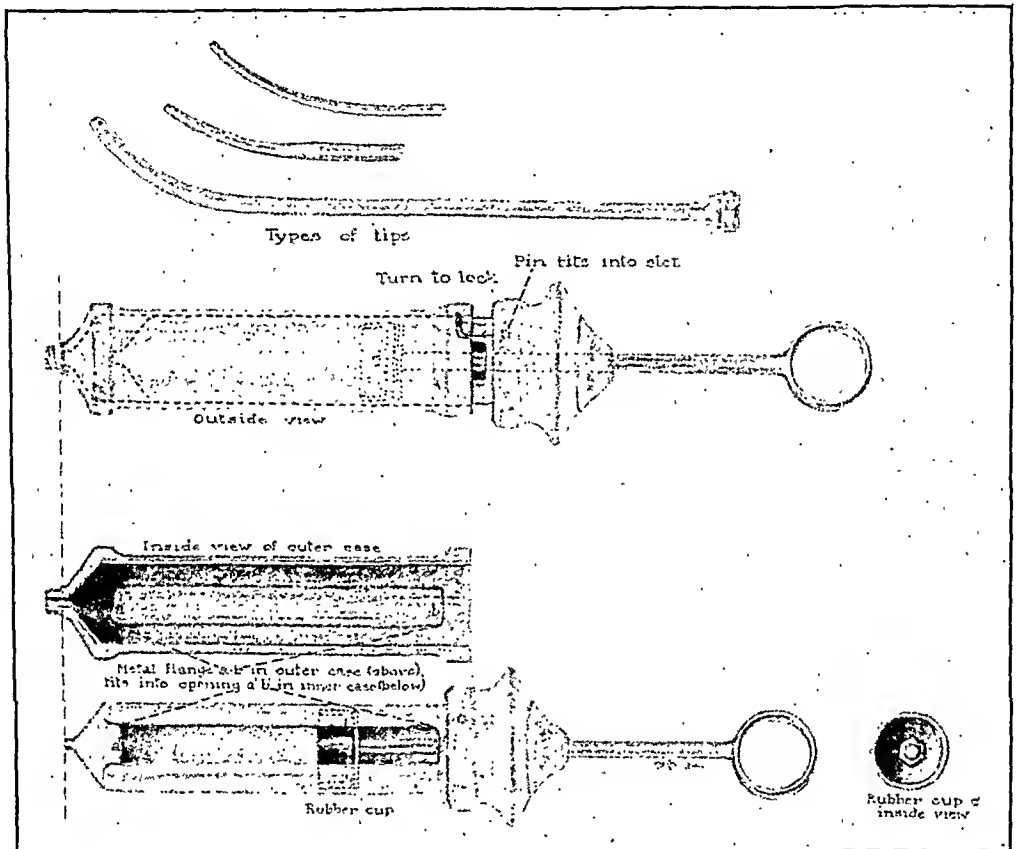


Fig. 1.

ficient jelly being injected to fill the cervical canal. Capacity of the inner barrel is sufficient to contain treatment for several patients with the tips detachable and boilable, so that one-half dozen or more patients may be treated in rapid succession from a single loading of the instrument.

The instrument may be taken apart and washed easily. Owing to the easy solubility of the medium used, water is quite sufficient for cleansing the syringe. Such an instrument, therefore, is ideal for dispensary use, being easily loaded, cleaned and ready for repeated use. This instrument we have found very convenient in office as well as in dispensary practice. The instrument may be adapted readily to other locations or purposes where injection of an ointment by means of a syringe with a long nozzle is indicated.

and the recent demonstrations of reproductive physiology are reviewed in a consideration of the present understanding of the causes and mechanisms of the menstrual cycle and early reproductive phenomena.

In discussing the mechanism of the pregnancy test of Aschheim and Zondek, he differentiates between the gonadotropic hormones of the hypophysis and the placenta. The suggested hormonal control of origin of the onset of labor is reservedly speculated upon, a diagram outlines the present concept of the mechanism of gland control. The probable factors in the mammary gland reaction after labor are described; and Kurzrock's clinical use of the anterior hypophyseal hormone, prolactin, is mentioned. Stander is candidly reserved in his acceptance of many of the newer theories of hormonal influences but feels there is a strongly suggestive biologic significance in many phenomena of obstetrics.

The chapters on the physiology, mechanism, and conduct of labor leave little to be desired. A commentary on the contributions to this phase of obstetrics is seen in the inclusion of not over a dozen references from the literature in the past five years in the appended bibliography. The methods of conduct of labor of the New York Lying-In Hospital are included here. Stander reviews the newer preparations of ergot derivatives but expresses no opinion, due to lack of clinical experience, as to their advantages over the older preparations.

In this section appears a new chapter on amnesia, analgesia, and anesthesia in labor, in which the history, agents, action of the drugs and various technics now in use, with their contrasted advantages and disadvantages, are discussed. Apparently the barbiturates are enjoying a swing on the pendulum of popularity, yet Stander regards the almost inevitable excitation consequent upon their use as an objectionable feature, and cannot regard them as ideal analgesics for obstetric cases, alone or in combination with other drugs; he personally limits their use to a very small and carefully selected group. His preference is evidently stated in the choice for his clinic practice of morphine and scopolamine, supplemented by ether and oil by rectum, and by nitrous oxide and oxygen during delivery and repair in the average case.

The section on obstetric surgery is clear in detail of technic, well illustrated, and conservative as to indication. The discussion of cesarean section upholds the place of the low cervical section, the discussion on prognosis plainly displays the dangers of the promiscuous use of the abdominal route of delivery. As might have been expected the section on the toxemias of pregnancy, a subject on which Stander has written much, reflects his personal ideas and investigations. There is a full discussion of the theory and the many lines of treatment. Stander regards the early termination of pregnancy in the unimproving preeclamptic as a desirable measure, and for the convulsive toxemia uses a modified Stroganoff regimen. His treatment is of the conservative school.

The third new chapter in this edition discusses the nondegenerative, or the inflammatory, lesions of the urinary tract. Here in a section illustrated with a number of excellent urograms are discussed from a viewpoint of modern diagnosis and treatment the topics of pyelitis, cystitis, and ureteritis. The anatomy and physiology of the urinary tract in pregnancy are described. Other less frequent lesions as stricture, ptosis, and tuberculosis are also discussed. The various methods of bacteriologic research and of kidney function tests are detailed and evaluated.

There are many other evidences of revision which must remain untouched. In his revision of this long and deservedly popular volume, Stander has well preserved the original principles of scientific and conservatively practical obstetrics as written by J. Whitridge Williams, and at the same time has brought the text fully abreast of the advances in the subject to which he himself has made no more notable contribution than this revision.

—Philip F. Williams

The illustrations are unusually numerous for a book of this size (581 pages). They show careful choice in their selection, many of them derived from well-known sources to whom all due credit is given.

The author has admirably fulfilled his promise to write this book for the student and practitioner, who will find it both easy to study and to refer to, with clear-cut answers to the many questions which arise in the study and practice of obstetrics.

—R. T. Frank

Titus has written a book on *Management of Obstetric Difficulties*,² designed for obstetric specialists but also to appeal to the general practitioner who, after all, does most of the obstetrics throughout the country, as well as for obstetric internes and residents. It covers mainly the abnormal phases of obstetrics, leaving normal obstetrics to general textbooks on this subject.

The volume begins with the causative factors of sterility and their treatment. Apparently the author credits the results and interpretations obtained by Ogino and Knaus.

This is a well-arranged book with careful and conservative description of the manifold difficulties encountered in the practice of obstetrics. It deals with the diseases of the fetus, such as monstrosities, chorionepithelioma, hydramnion and oligohydramnion. A considerable portion is devoted to the diagnosis and treatment of abortion. The author advises prompt emptying of the uterus for missed abortion. He believes that the Friedman and the Aschheim-Zondek tests become negative ten days after death of fetus. A very complete discussion of ectopic gestation is given as well as that of placenta previa and premature detachment of the placenta. The various methods of operative obstetrics are described, including forceps, cesarean section and mutilating operations on the fetus.

Most of the maneuvers necessary throughout obstetric practice are carefully detailed, including methods of anesthesia, saline and glucose injections, as well as transfusion of blood. The book is excellently illustrated.

—R. T. Frank

Williams Obstetrics,³ a classic in obstetric literature and a standard textbook for a generation, appears in the seventh edition, five years elapsing since the previous revision. The revision and enlargement of the work has been made quite fittingly by H. J. Stander, who was long and closely associated with J. Whitridge Williams in the teaching and practice at Johns Hopkins Hospital. It is evident from a study of the book that the contributions to the literature of obstetrics as a speciality, for the past five years, have been evaluated with a singular discernment. One feels that such articles as have had their worth-while points incorporated in the rebuilding of the text or as have been included in the bibliography may well be regarded as of distinct merit in obstetric literature. The chapter bibliographies are thus relatively long, but this is in line with Williams' statement in the preface of his second edition that he wished to give full credit to all who had played a part in the development of obstetrics. The text has been increased by one hundred and thirteen pages, due to added material in a rearrangement of the former text and the inclusion of three new chapters on physiology, anesthesia and analgesia, and urological pathology.

In the first of these new chapters, Stander discusses the sex hormones and their relation to menstruation, pregnancy, parturition, and lactation. The known facts

²The *Management of Obstetric Difficulties*. By Paul Titus, M.D., Obstetrician and Gynecologist to the St. Margaret Memorial Hospital, etc. 879 pages, with 314 illustrations, including four in color plates. The C. V. Mosby Company, St. Louis, 1937.

³*Williams Obstetrics*. By Henrietus J. Stander, Professor of Obstetrics and Gynecology, Cornell University Medical College, etc. Seventh edition, a revision and enlargement of the text originally written by J. Whitridge Williams. With 278 illustrations and 1269 pages. D. Appleton-Century Company, New York, 1936.

Dr. McIlroy regards the theories and classification as still incomplete and poorly founded. She suggests further research on the endocrine aspect and the deficiency origin of this condition. In discussing symptoms and signs of toxemia, she feels that they are, for the most part, effects of altered metabolism on the various systems and organs and represent the degree of increasing recessions of defense.

Chronic nephritis in pregnancy is considered as an entity and forms the subject of a very able section, as does also the contribution of her coworker, Jane McIlroy, on the eye changes of toxemia. Dr. McIlroy emphasizes the importance of antenatal care and prophylaxis and stresses the conservative medical treatment with obstetric interference, practiced only when indicated.

This very excellent presentation of the subject should be in the hands of all obstetricians.

—Philip F. Williams

Siedentopf in his monograph *Die Bekämpfung der eklamptischen Schwangerschaftserkrankungen*⁶ gives us a wide discussion of the modern views on the prevention and treatment of the late pregnancy toxemias. Basing his study upon the clinical material of the Leipzig school, supplemented by his researches in physiological chemistry during his postgraduate work in the United States, and a critical review of the recent literature, he offers a very thorough consideration of this difficult problem.

Siedentopf, remarking upon the prophylaxis of the condition, under the caption prenatal care, states that 300 deaths occur in the 2,000 eclampsias met annually in Germany, and refers to the very high death rate from the disease in the United States. The subject of antenatal hygiene is meticulously detailed. The treatment of preeclampsia, he insists, should be directed along conservative lines toward avoidance of eclampsia; yet his attitude toward the use of cesarean section is eminently sane. Siedentopf discusses the therapy of the three lines of treatment, active radical, conservative, and middle line, from many angles. There are chapters of merit on the late effects of toxemias, and of their recurrences. In the conclusions the author states that so long as the etiology remains undiscovered and as long as there is no clear causal therapy our best defense against the toxemias is a constant and increasing effort against their occurrence.

This, the first German monograph on the subject in ten years, is a splendid presentation on the prevention and treatment of the toxemias and deserves to be widely read.

—Philip F. Williams

*Therapeutica das Syndromes Gravido-Puerperales*⁷ (*Treatment of the Gravid-Puerperal Syndromes*) by J. P. de Camargo in its second edition is a relatively short book whose material is presented in an easy-assimilable form.

A great variety of complications which may occur during pregnancy are discussed from the standpoint of etiology, symptoms, prognosis, and treatment. They include such widely diverse subjects as pernicious vomiting, varicose veins, infections, tuberculosis, chorionepithelioma, hydramnios, and many others.

Throughout, the author's point of view is sane and practical, and the information given is short and concise. The only faults to be found are the almost complete ab-

⁶*Die Bekämpfung der Eklamptischen Schwangerschafts-Erkrankungen.* Von Heinrich Siedentopf, Oberarzt der Universitäts-Frauenklinik zu Leipzig. 86 Seiten. Johann Ambrosius Barth, Leipzig, 1936.

⁷*Therapeutica das Syndromes Gravido-Puerperales.* Par Dr. Joao Perelra de Camargo, livre docente de medicina da Universidade do Rio de Janeiro, etc. 2.^a edição correcta e muito augmentada. 376 pages. Freitas Bastos, Rio de Janeiro, 1936.

This book, *A Manual of Practical Obstetrics*,⁴ has been written to present the subject of Clinical Obstetrics in as practical a form as possible. It is felt that the author has succeeded very well in his effort. He has left out statistics and theoretical considerations largely and has expressed very definitely his own views and methods of handling difficult situations. The illustrations which are borrowed in part from other works serve well to illustrate the text.

Anatomy and physiology are briefly discussed. Antenatal care is gone into in much detail; here as in other sections of the book there seems to be a considerable tendency to recommend proprietary medicines by name. In discussing the diseases complicating pregnancy the author does not mention the use of early cesarean section in diabetes, a procedure which is often used in this condition in the United States. The directions for the conduct of pregnancy, obstetric diagnosis, mechanism and conduct of normal labor, care of the patient during labor are gone into thoroughly, simply, and concisely, with practical suggestions. The lateral position suggested is not in use in the United States and the frequent interspersing of illustrations of patients in the dorsal with those of patients in lateral positions are confusing. The author does not favor rectal examinations in labor.

A rather marked error in proofreading occurs on page 66; "Sometimes it is more convenient to remove the baby before stitching a torn perineum." In the able chapter on stimulants and anesthetics of labor, the barbiturates are not mentioned. Follow-up examination over a sufficient period of time is stressed in the care of the puerperal patient. The abnormalities of labor, hemorrhages, and the treatment of various complications are well presented. The author evidently feels that cesarean section has not been employed with sufficient frequency in Ireland for placenta previa. The Rotunda method of treating convulsive toxemias of pregnancy is the author's choice. The Stroganoff treatment is also described. There is a fine chapter on puerperal sepsis.

The book concludes with three chapters written by colleagues, one on the New-born Infant by Collis, which is a fine presentation; a chapter on Radiology written by McDonogh which stresses the importance of roentgen ray examinations in obstetrical practice and a concluding discussion of Blood Typing and Blood Transfusions by Dockeray.

This is an excellent presentation of practical obstetrics, a working manual, eminently suitable for the general practitioner.

—Philip F. Williams

An ill-defined symptom-complex, *The Toxaemias of Pregnancy*,⁵ forms the subject matter of this very thorough and comprehensive review of the literature and discussion of the many problems encountered in the prevention and treatment of this state of altered metabolism in pregnancy. Dr. McIlroy is to be congratulated upon the thoroughness with which she has reviewed the world-wide literature of the problem and the splendid arrangement which she has made of this material. As a review it presents the findings, facts, and opinions from every country with the exception that German literature is seemingly incompletely covered.

The book takes up the statistical aspect of the subject stressing maternal and fetal mortality, then covers the theories and classifications and follows with the functional studies of the normal and abnormal pregnancy. Antenatal care is exhaustively studied under the subjects of nutrition, diet deficiency, and relation of weight changes of toxemias.

⁴*A Manual of Practical Obstetrics*. By O'Donel Brown, Assistant Gynecologist, Sir Patrick Dun's Hospital, Dublin, etc. With 10 plates, some in color, and 236 illustrations, 363 pages. William Wood & Company, Baltimore, 1936.

⁵*The Toxaemias of Pregnancy*. By Dame Louise McIlroy, Consulting Obstetrician and Gynaecologic Surgeon, Royal Free Hospital, etc. 355 pages. William Wood & Company, Baltimore, 1936.

The influence of diet upon the vitamin content of the human breast milk and upon the development of the suckling is discussed. The relations of various influences, especially hormonal, upon the three phases of breast secretion are brought out.

There is a short section upon the vitamin content of the milk from the breast of the newborn. The conclusions summarize the vitamin needs of the nursing child compared with the vitamin content of human and cow's milk, and give valuable suggestions as to possible alterations in certain deficiencies of one or the other vitamins under such conditions in the mother as a previous pregnancy-toxemia in a suspected rickets of the newborn.

This subject is barely touched upon in the majority of textbooks of obstetrics, and the material here presented fills an undoubted gap in this phase of our care of the lactating woman.

—Philip F. Williams

This report of the *Proceedings of the First All-India Obstetric and Gynecological Congress*,¹¹ Madras, will be of interest to those who are concerned with the practice of Obstetrics and Gynecology in a country with so many types and customs in the social life as the people of India present. It should mark, too, an important beginning for the further developments of the specialty of Obstetrics and Gynecology in that country where today but one university, Madras University, is able to give postgraduate training in these subjects. In opening the Congress, Lord Ersking, Governor of Madras, paid special attention to the question of maternal mortality.

The material presented at the Congress followed three main topics: the third stage of labor, featuring papers on postpartum hemorrhage, placental pathology, and treatment of retained or adherent placenta; the second topic considered the subject of pelvic disproportion in its various aspects. There were presentations in this symposium on reviews of cases of dystocia, management of labor in contracted pelvis, cesarean section in infected cases, and a very able paper on the lower segment operation. It is evident that the advantages of the lower segment operation are well known in India, although it has not been performed extensively and the author summarizes by remarking: "This is an operation that has, in my opinion, come to stay; is a powerful weapon in our obstetrics armamentarium and has its maximum utility in controlled test labor cases." He remarks, however, that the actual performance of the procedure is outside the province of the occasional operator.

The gynecologic topics include a review of the use of radium and a discussion of the five-year cure of cancer of the cervix. Papers were presented on antenatal care, and on organization and conduct of child welfare schemes, and on infant mortality. The very timely paper on the value of postnatal care in which the author makes a plea for the establishment of postnatal clinics throughout India closes the proceedings. The topics selected for discussion in the next All-India Congress are Toxemias of Pregnancy and Cancer of the Cervix.

—Philip F. Williams

*Being Born*¹² is a short, attractive little book for boys and girls of the late grammar school and early high school age. The information it contains is very carefully and interestingly presented, with clear-cut, good illustrations describing all the processes connected with reproduction. Nobody who reads this will for a moment doubt the sincerity, wide experience and pedagogic skill of the author.

¹¹First All-India Obstetric and Gynecological Congress, Madras; January 2 to 4, 1936. Proceedings.

¹²*Being Born*. By Frances Bruce Strain. 144 pages. D. Appleton-Century Company, New York, 1936.

sence of illustrations as well as the tendency toward the utilization of hormonal preparations where their value may be doubtful, as in the pernicious vomiting of pregnancy. A better correlation of the material would also improve the book.

—Frank Spielman

This is a large volume⁸ by numerous authors and is published by the Obstetric and Gynecological Clinic "Luigi Mangiagalli" of Milan in memory of the thirtieth anniversary of its foundation, and dedicated to the memory of Mangiagalli. The first paper is by Alfieri, the Director of the Clinic, who reports on 7,000 laparotomies performed between the years 1927 and 1936. Of these patients only 325 were operated upon per vaginam. The total mortality in the 7,000 was 3.55 per cent. Of the numerous articles there is one on embolism and thrombosis after operation, another dealing with 57 cases of hydatid mole and 8 of chorionepithelioma. Considerable space is devoted to Alfieri's method of shortening the round ligaments for retroflexion by laparotomy. The ligaments are cut across at their uterine end and the free end then implanted into the posterior surface of the uterus after having been passed through the broad ligament below the utero-ovarian ligament, somewhat in the manner of Webster-Baldy. The huge activities of the clinic are fully described in this monograph in which very careful attention to the literature, with bibliographic references, has been given.

—R. T. Frank

Staehler in *Arbeitsphysiologie der Schwangerschaft*⁹ discusses the energy output of labor, the respiratory changes during labor and the effect of the various types of physical activity during pregnancy.

He has measured for the first time the energy output of labor in calories and states that a single contraction produces an average of four calories and that the highest production which he has measured was equivalent to a thirty-kilometer march; comparisons are made between the work of labor and of various occupational stresses.

The respiratory exchange of normal pregnant and parturient women was studied from a standpoint of frequency and volume of the respiratory excursions. Staehler discusses the minute volume interchange during the dilating and expulsive stages of labor, and the variations caused by various reflex phenomena. The effect of physical work in pregnancy was studied in relation to the influence it had upon physiology of the circulatory system. As might have been expected moderate exercise was found beneficial and extreme degrees of physical exertion were dangerous.

This is an interesting contribution to the physiology of pregnancy.

—Philip F. Williams

In *Die Vitamine der Milch*,¹⁰ Neuweiler takes up the physiology and relationship to various phases of metabolism and stages of development of the known groups of vitamins. He then reviews the researches which he and other investigators have made upon the vitamin content of human and cow's milk. There are two colored photomicrographs to illustrate the demonstration of vitamin C in the lactating mammary gland.

⁸Nel Trentesimo di Fondazione, Della R. Clinica Ostetrico-Ginecologica "Luigi Mangiagalli" di Milano. 956 pages. Pidenza. Tipografia Adamo Mattioli. 1936-XIV.

⁹*Arbeitsphysiologie der Schwangerschaft*. Von Dr. Med. Fritz Staehler, Oberarzt an der Universitäts-Frauenklinik in Frankfurt a.M. Mit 16 Kurven und 17 Abbildungen im Text. 103 Seiten. Verlag von S. Karger, Berlin, 1936.

¹⁰*Vitamine der Milch*. Dr. Med. Walter Neuweiler, Universitäts-Frauenklinik, Bern. 140 Seiten. Verlag von Hans Huber, Berlin, 1936.

not a volume designed for general reading but rather as a source book which embraces the most important and valuable contributions to this rapidly growing subject. It will be much appreciated by all others working in this same field.

The anatomy of the pituitary body is of course first considered. The effect of hypophysectomy and the results obtained with growth-promoting and gonadotropic extracts are taken up, as well as the lactation factor. Next the interrelationship between the pituitary and the other endocrine glands is considered. The physiology of other portions of the hypophysis, namely the pars intermedia and the pars neuralis, are described. A short appendix gives the scientific and commercial names of hormones as well as structural formulas of such hormones as have been identified.

—R. T. Frank

*Endocrinology in Modern Practice*³⁴ by Wolf has been written with the aim of supplying the practitioner with a textbook, "free from burdensome, technical and theoretical discussions," of clinical endocrinology. This book appears to be based largely upon study and adaptation of the enormous literature which has accumulated during the last decade rather than upon clinical experience. It is carefully planned and consistently executed. For each gland an introduction containing the anatomy, embryology, histology and, as far as known, biology and physiology, has been given. The fully worked out syndromes are well described. The diagnosis is clearly dealt with. Each chapter is concluded by a tabulated summary which gives a comprehensive view of the individual glands and their diseases. Good judgment has been displayed in not beclouding the issue by emphasis of the so-called pleuriglandular syndromes.

The contents of the book covers the pituitary gland, the ovaries, testes, thyroid, adrenal, parathyroid, thymus, pineal, the mammary gland, pancreatic islands, "other hormones" which include the liver, stomach, duodenum, pancreas, spleen, kidney, heart, placenta, hormones of the nervous system and antihormones. The author then takes up obesity, menstrual disorders, and the menopause and sterility. A large portion of the book is devoted to endocrine aspects of "non-endocrine" diseases which cover such diverse matters as pre- and postoperative considerations, suppuration, surgical and orthopedic diseases, the diseases of children, and of every one of the systems contained in the body.

An entire division of the book deals with endocrine diagnosis, including a comprehensive description of the interpretation of laboratory findings as well as diagnostic and laboratory procedures. A regional symptom diagnosis is given. A short chapter on endocrine preparations and their use concludes this volume of 1,018 pages.

There is no question that much of value has been gathered by the author; that he has kept in mind the limitations of the general practitioner in his knowledge in this field. The lucidity of his descriptions is admirable. His study of the literature is amazing in its completeness, although the lack of references makes investigation of the sources almost impossible.

A tremendous amount of material, unrelated to the subject of endocrinology, however, frequently confuses the issue. In some ways the book reminds me of Hare's *Practical Therapeutics and Diagnosis of Diseases*, but unfortunately our present state of knowledge makes me feel that this attempt is premature.

Lack of available space prevents my giving a complete review of the book. Under the pituitary diseases, syndromes, as yet not understood, are given, such as achondroplasia, adiposis dolorosa, Schüller-Christian disease, Mongolism, and Laurence-Biedl syndrome. The same applies to every other chapter which adds greatly to the size of the book.

Innumerable loose statements can be taken issue with. For instance, a third ovarian hormone "relaxin." Investigation has shown that this "relaxin" action

³⁴*Endocrinology in Modern Practice*. By William Wolf, M.D. With 252 illustrations and 1,018 pages. W. B. Saunders Co., Philadelphia, 1936.

This book, if put in the hands of boys and girls, will help parents in having the facts of life presented in a wonderfully clear-cut fashion, in such a way that they need not dread the reaction of any normal child to this enlightenment.

—R. T. Frank

Pediatrics

The title page informs the reader that this book, *The Baby and Growing Child*,³¹ is for physicians, mothers and nurses. The reviewer fails to discover much in the text of any value to the physician.

The best part of the publication is the illustrations.

There are some inaccurate statements, or at least questionable ones, which the author makes with some positiveness. For example, at the bottom of page one he starts the sentence which reads as follows: "The moment a woman reduces her weight by eliminating or reducing food, she automatically reduces the weight of the unborn infant," and again on page four he writes, "Shock, fright and sudden excitement during pregnancy may cause psychic disturbances in the newly born."

There is much useful information in the book but the uninformed reader, presumably the mother, would be unable to discriminate and be guided by that which is generally accepted as the best available opinion based upon our present knowledge.

It is difficult, perhaps impossible, to write a book which could harmonize varying ideas and practices. Probably no author could write a manual which would serve the threefold purpose of serving physicians, nurses and mothers. It would doubtless have been much better for Dr. Louis Fischer to have written a book with the single purpose of informing mothers.

—Fred L. Adair

Out of his unusually rich experience as a practicing pediatrician, the author has given the nursing profession a very valuable and practical textbook.³² As usual in the writings of the author, he follows the simple, common sense attitude and prefers the tried methods to the experimental and theoretical ones. The book is divided into two parts: the first called "The Science" and the second "The Practice." In the first 26 chapters there is a concise summary of the essentials of pediatric knowledge for the use of nurses. In the final 22 chapters the practical application of this knowledge is discussed. As usually happens a strict separation of theory and practice is not quite possible. On the whole we agree with most of the statements of the author, but the chapter on child psychology could have been written along more useful lines. The instinct psychology of MacDougall's is not exactly the best foundation for child psychology. We would have liked to see an additional chapter on mental hygiene of childhood as applied to the work of the nurse.

—P. J. Zentay

Endocrinology

A very important contribution to endocrinology is *The Physiology and Pharmacology of the Pituitary Body*³³ by H. B. Van Dyke, now Professor of Pharmacology, Peiping University Medical College, China. The book is based on a huge and readily accessible bibliography which includes references to the year 1935. It is

³¹*The Baby and Growing Child. Feeding and Health Care.* By Louis Fischer, M.D., consulting physician of the Willard Parker Hospital, New York City, etc. Illustrated, 260 pages. Funk & Wagnalls Company, New York City, 1936.

³²*Pediatric Nursing.* By John Zahorsky, M.D., Professor of Pediatrics and Director of Pediatrics, St. Louis University School of Medicine, with 144 illustrations in the text and 7 color plates, 568 pages. The C. V. Mosby Co., St. Louis, 1936.

³³*The Physiology and Pharmacology of the Pituitary Body.* By H. B. Van Dyke, Professor of Pharmacology, Peiping Union Medical College, Peking, China. 577 pages. The University of Chicago Press, Chicago, 1936.

- E. EVERETT BUNZEL, New York, N. Y.
 BERTRAM HARRINGTON BUXTON, Providence, R. I.
 EUGENE SEELEY COLER, New York, N. Y.
 MILTON ALFRED DARLING, Detroit, Mich.
 D. ANTHONY D'ESOP, New York, N. Y.
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 SAMUEL GOLDSTEIN, Pittsburgh, Pa.
 JACOB GOLDSTEIN, Toronto, Canada
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 RICHARD TORPIN, Augusta, Ga.
 EMANUEL MANNING WAINESS, New York, N. Y.
 VICTOR G. H. WALLACE, Norwalk, Conn.
 ARTHUR J. WALLINGFORD, Albany, N. Y.
 JOHN G. WALSH, Providence, R. I.
 GEORGE W. WATERMAN, Providence, R. I.
 JAMES M. WHITFIELD, JR., Richmond, Va.
 ALLEN PELLINGTON WINSOR, Boston, Mass.
 L. BURDETT WYLIE, Lakewood, O.

is ascribable to the estrogenic hormone. A statement that vitamin A and E deficiencies are "undoubtedly" responsible for a number of instances of hypoovarism. The author's views on the efficacy of testicular transplants from other species can certainly not pass muster. As long as this book aims to be so complete, scleroderma and Raynaud's disease should be described under parathyroid disturbances. Who will agree with the author that lipoma is "caused by faulty fat metabolism"?

—R. T. Frank

Correspondence

To the Editor:

Shortly after the publication in the July, 1934, issue of the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY of the article "*An Endometrial Theory of Ectopic Pregnancy and an Intraligamentous Pregnancy at Six Months*," written by Schenck and Frankel, I received a letter from Dr. J. B. Dawson, Professor of Obstetrics and Gynecology in the University of Otago, Dunedin, New Zealand. He drew to my attention an article on *Ovarian Pregnancy* which had been published by him in the *Medical Journal of Australia* for August 21, 1926, in which he had advanced the suggestion that an explanation of the occurrence of ectopic pregnancies may be found in the presence of ectopic endometrium in the ovary, tubes or pelvis, exactly the same theory independently arrived at and advanced by us in the article mentioned above.

In our article, due to an oversight, no reference was made to the paper of Dr. Dawson's, and his name was omitted from the list of references.

SAMUEL B. SCHENCK.

Brooklyn, May 29, 1937.

Items

American Gynecological Society

Officers for 1937-1938

Dr. N. Sproat Heaney, *President*.

Dr. Norris W. Vaux, *First Vice-President*.

Dr. Frederick C. Irving, *Second Vice-President*.

Dr. Richard W. Te Linde, *Secretary*.

Dr. William C. Danforth, *Treasurer*.

Dr. Fred J. Taussig (4 years), Dr. Philip F. Williams (1 year), and Dr. Harold O. Jones (1 year), *members of Council*.

American Board of Obstetrics and Gynecology

Diplomates Certified by the American Board of Obstetrics and Gynecology, Inc., June 7 and 8, 1937, Atlantic City, N. J.

MERVYN V. ARMSTRONG, Brooklyn, N. Y.

RUPERT E. ARNELL, Chicago, Ill.

VITUS WILLIAM BADIA, New York, N. Y.

GEORGE GORDON BEMIS, New York, N. Y.

JOSEPH PHILIP BENSON, Punxsutawney, Pa.

GEORGE J. BERSON, New York, N. Y.

GEORGE LOVERIDGE BOWEN, New York, N. Y.

JAMES N. BRAWNER, Jr., Atlanta, Ga.

JOHN CARLISLE BROWN, Atlantic City, N. J.

Words fail me when I attempt to express my personal appreciation and also my appreciation of the Society's influence in behalf of our specialty in Kansas City. I only trust that you will believe me when I say I thank you.

Sentiment passes into insignificance when I recall that this Society was organized for a definite purpose and that from year to year it has carefully chosen its members to carry out this purpose. This Society is an offspring of illustrious parents—The American Gynecological Society and the American Association of Obstetricians, Gynecologists, and Abdominal Surgeons. These Societies have been very much interested in our activities and are interested in those members of this Society who might qualify to carry on the future activities and the traditions of the parent organizations.

At the christening of the Central Association, its future activities were dedicated mainly to the improvement of obstetrics in this section of the United States. Its sponsors were men whose horizon has been international, whose judgment sound, whose advice wise, and whose achievements class them as the noblemen of our specialty.

The previous leadership in this Society has been drawn from men well known in American obstetrics and men whose efforts have always been for the improvement of obstetrics.

The yearly meeting is an inherited custom of the parent organizations. The papers with their discussions represent the clinical and research progress made each year. These meetings have served still another important function, that of developing warm friendships. Such friendships serve not only to break down sectional barriers, but also serve to develop a oneness of thought and purpose. Such a leadership, with such a membership, so efficiently organized, should be eminently fitted to carry out the purpose for which the Society was organized; namely, the improvement of obstetrics in this special area.

A survey of the area with its problems brings out some interesting facts. Foremost are the criticisms made against American obstetrics. Our first impression is to be offended when criticisms are made and only tangible facts can change impressions. These facts are well borne out in the reports of the White House Conference and to a lesser degree in the reports from our own Society made in the last two years. Fortunately we have strong allies in the parent organizations and the American Committee on Maternal Welfare. It would seem that one of the first efforts of the individual member of this Society would be to see that his state has a strong maternal welfare committee, and that this committee would function with the State Society and the State Medical authorities in making each state committee efficient, to the end that all state committees would cooperate with Dr. Adair's committee for the improvement of obstetrics. From personal experience in the last two years in my home state, Missouri, I know it can be done and I would

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Central Association of Obstetricians and Gynecologists

FEAR*

PRESIDENTIAL ADDRESS

BUFORD G. HAMILTON, M.D., KANSAS CITY, MO.

LIFE would be a very drab existence were it not for our friends. It is the pleasures derived from association with friends, the unexpected kindnesses of friends, that silent understanding that exists between friends and doing for others that make life worth while.

This Society holds pleasant memories for me that will always be a sustaining stimulus for my own endeavors. I was present at the meeting in St. Louis when this Society was organized, and was made a member of the first executive committee. The first scientific meeting was held in Kansas City, for one day, in connection with the Kansas City Southwest Clinical Society. In the morning exclusive obstetric and gynecologic clinics were held in all the leading hospitals of greater Kansas City. In the afternoon, papers were given by distinguished members of this Society before some 1,000 general practitioners representing 22 states. This was pleasing to the founders of this Society since it was truly a missionary introduction for the Society in this area. This meeting was of special interest to the members of our specialty in Kansas City, since it was an opening wedge that separated obstetrics and gynecology from surgery in some of our hospitals.

At the meeting in New Orleans when you did me the very great honor to name me as your president for this year, I must confess I was deeply moved, since it is a great privilege to represent such a group as this one.

*Read at the Eighth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Detroit, Mich., October 15 to 17, 1936.

NOTE: The Editor accepts no responsibility for the views and statements of authors as published in their "Original Communications."

of Eden he was surrounded with all that man could desire. However, the Master denied him one fruit, and as we know, he failed. Then it is recorded that when the Master asked him why he had not been equal to his one trust he replied, "I was afraid." All may not agree with this philosophy but rather with Williams who, when attempting to analyze human behavior said, "What reason should correct, all the training in the world will not improve a weak endowment."

As we attempt to define fear we may go far into the scientists' theories, most interesting yet confusing, especially so when we attempt to compare human behavior with obstetric behavior. A common conception of fear is that it is the response of an organism to a stimulus that may be injurious or destructive.

We are convinced from observing the prenatal, the natal, and the postnatal care of women that the problem is both moral and scientific. From this point of reasoning, we would suggest that fear is an inherited or acquired conception of right and wrong as is found in the philosophy of the teachings of the Master, that of doing unto others as you would have others do unto you.

From observing the attitude or the human behavior of physicians, we frequently assume that inheritance is the determining factor in their professional or obstetric reactions, yet as we observe the influence of environment, we finally conclude that both inheritance and environment are necessary for the development of the physician. Adair has suggested that the prenatal period should begin with the preconceptive period. From this philosophy we would suggest that doctors are born and not made, and that they are born of generations of integrity, of citizenship, and those accomplishments that contribute to the happiness and benefit of others.

Fear as applied to obstetric behavior might be said to be of two types: First, a trained, an intelligent, a reasoning, a courageous fear, and a fear for the right. Such fears have only one objective, the well woman and her well baby. Second, the untrained, the ignorant, the weak, the oscillating fear and the lack of fear for wrong—such fears are responsible for the invalidism of women and the loss of women and children. In its practical application it means that the trained, reasoning, courageous fear and the fear for right can only be influenced by errors of judgment. Such fears develop obstetric curiosity, investigation of problems or research, and an interest in everything that pertains to the improvement of obstetrics. The greatest enemy, the greatest obstruction, the greatest danger to maternal welfare is the weak, oscillating, thoughtless, ignorant, or wrong fears of both the trained and the untrained. If we are to search for the real offending organism that will grow, that can be placed into one definite group and proved by comparison, we would say that this wrong fear represents the offending organism in American obstetrics.

emphasize the importance of cooperating with the State Medical Society and the State Medical authorities as a basis for efficiency. I can also assure you of the helpful assistance of Dr. Adair and his associate.

The members of this Society are known as specialists. Every state and county society and every hospital, indeed every woman in this area can be influenced and directed by the teachings and practice of this membership.

Critical as the statement may seem, I believe that we should accept the challenge that American and sectional maternal welfare problems belong to the specialist. As such we become the liaison between the medical school and the general profession in the improvement of obstetrics.

This becomes the more important when we review the activities of the American Board of Obstetrics and Gynecology. Each year this board, in qualifying those who may be called specialists, is making the requirements more stringent and is stressing the importance of the specialist's relation to the general practitioner. Therefore, it is of first importance that every member of this Society become a diplomate that he may have greater influence in his community.

Something of the magnitude of the undertaking of this Society may be appreciated when we recall that this area has a population of fifty-nine million people who represent our most typical American stock.

There are 16,089 doctors and 3,038 hospitals to care for this population. Then there are 37 medical schools that teach and train more physicians and specialists than any other similar area in the United States. Such a problem with such possibilities requires a beginning and an objective. Our beginning must be the individual physician or specialist and our objective the well woman and her well baby.

From a teaching viewpoint it is most difficult to analyze the teaching of students and their reactions to their training in private practice. It has been most fascinating to observe human behavior and obstetric behavior of both the physician and the specialist when accepting the responsibility for the care of expectant mothers. It would seem from the hours given for the teaching of obstetrics and the character of the teaching given that reason would obtain at all times. On the contrary there seems to be a particular emotion that supersedes reason where responsibilities are assumed. This emotion from its manifestations is recognized as fear. Many times when obstetric problems are discussed the statement is made that too often fear rather than reason directs procedure. For several years I have been an associate of students as an instructor, an associate of internes as a staff attendant, and an associate and consultant of the general profession. Often members of each of these groups when faced with obstetric responsibilities and defending a method or a procedure have justified their conduct by saying, "I was afraid." It may be said that this is only an inherited human weakness, since it is recorded that when father Adam was placed in the garden

must judge his ability by his grades." The real boy cannot be measured by this method and I question the type of doctor developed from such an environment.

The premedical subjects are inspiring when presented by inspiring teachers. Unfortunately too often these subjects have become illegitimate subjects of illustrious parents and are presented by intellectual inebriates whose only marks of distinction are alphabetical notations. From many internes and recent graduates, we are told that certain ones of these emphasize the fact that their judgment of students determines the future doctors from that school. Unfortunately this attitude from an academic dialysis has escaped into the first two years of medicine. We find that for six years the would-be doctor is exposed to this environment and that he does not come in contact with doctors but for two years or at the most for two and a half years.

Another tragedy in developing doctors arises from the practice of certain schools accepting more students in the freshman year than can be cared for in the sophomore year. Their freshmen know that judgment is not passed on them by doctors but by the test tube, microscopic and academic would-be makers of doctors who judge too often from grades. May I ask what type of fears, what type of attitude toward human beings can be developed from such an environment? If hopes, honor, ambitions, and sentiments are stunted or paralyzed in attempting to make grades, only a sterile or materialistic attitude toward maternal welfare problems may be developed.

After graduation, internships become a most serious problem for both the school and the student. It would seem that when all schools require one year's internship before graduation and when hospitals are supervised by our national boards the problem will be solved. At the present time the private hospital internship in far too many instances is only an observation course. The lack of supervision and the lack of a common head develop false conceptions and habits that are important factors in our maternal welfare situation. We are having internes who before coming to our private hospitals have never been present at a home delivery. In a few instances we have had internes who have not so much as delivered one woman in the home or in the hospital. It is not infrequent in private hospitals without a clinical service that the interne will not deliver one woman while on the obstetric service. Somewhere in our course of training, students and internes must be required to follow patients through the entire course of labor, or the clinical course of labor cannot be known. It is my humble opinion that the one weak point in our training of students and internes is that not enough stress is placed on demonstrating the clinical course of labor, for it means staying at the bedside of patients during the entire course of labor. This is impossible in the unsupervised private hospitals

Take, if you will, the development of the physician and follow the possibilities of the two types of fears, especially those influenced or developed from environment. From infancy through primary school and high school, parental affections, discipline, and example develop courageous fears that direct behavior. From high school to the college or university is an epoch. A newly found freedom is encountered, an expression frequently made by students. In starting into medicine so many premedic hours are required and so many cultured hours are taken for an academic degree. Dr. Hutchins, president of the University of Chicago, has said that "The first two years of college work should be taken at junior colleges and at home, and if the student shows sufficient ability the last two years may then be taken in the university." This is a timely suggestion since home environment and home discipline are far superior to the influence of the so-called newly found freedom of the university. Then may I suggest that only the cultured hours be taken in the junior colleges, since many educators have suggested that few students know what profession to choose for their life work before their junior year. Also the parent may or will be cognizant of the situation and both time and money may be saved and disappointments avoided. The two years of home training and the added age will, without doubt, better fit the future doctor for premedical and medical training. Besides, as I will discuss later, we feel that the medical school should assume the responsibility for choosing those qualified to study medicine. The future doctor entering the university is the greatest idealist known, just clay, but how important the molding, since from the model is made a doctor or a specialist, of bronze, of marble, or of plaster. Again how important, since when placed in its permanent location, its beauty and its stability influence the professional, cultured, social, and spiritual life of that community.

Recently two nationally known medical educators were discussing this subject. The younger man's son was graduating from high school with high honors. The son had chosen a university described by his father as having an unusual social life. He spoke of the classes as being large and how impossible it would be for the professors to know the individual student. He also mentioned that the university was known for the friendships made on the campus and this influence on the financial future of its graduates. After this description of this university he asked this question, "If my son has the ability he seems to have, where would you send him for his university work, looking forward to his studying medicine?" The older man answered, "I sent my sons to a small university, where they had inspiring teachers and where the teachers knew my sons personally." It is of interest that his sons have both made superior records. He then made this very significant statement, "Your son's choice without doubt will be a great factor in his making money. His teachers, not being able to know him personally,

logic reactions. Certainly we sympathize with the fears of the recent graduate and even with the recently trained specialist. It has always been of interest to me to note that the better training the physician has had the greater his fears have been.

The story is told of a distinguished obstetrician who was visiting a colleague in a neighboring city. At that time the colleague had a patient in labor with a posterior position. The membranes had ruptured prematurely, the cervix was hard and only partially dilated after twenty-four hours of pain with rest periods. However, the patient was in good condition. Later in the day the patient became tired, the pulse was 120, the head at the midstation, rotation was not completed, the cervix not completely dilated, and the host then asked his colleague to examine his patient and tell him what he thought best for the patient. This was done and the colleague advised to wait. The host, being tired and seeing how prolonged labor had been, said, "I have given the patient several rest periods. Do you think it is safe to wait?" Again the advice was for rest and to wait and still again if necessary. Later the patient delivered safely with the mother and child in good condition. The story appealed to me for three reasons. First: because these two nationally known teachers with large clinical experience were deeply concerned over a patient with a posterior position. Second: because the host appreciated the possibility of errors in judgment when tired and was amenable to advice and suggestion. Third: because they both had thorough training and experience, that rare virtue of decision to wait, and that trained courageous fear for the future health of the patient. Then it occurred to me that these are the attributes in physicians that determine their right to be classified as specialists and teachers of medical students.

It is agreed that the greatest number of women are being delivered in their homes and the question is being seriously asked, Can a woman be delivered as safely in the home as in the hospital? All would welcome the day when all women would be delivered in a hospital, but since the majority of women are delivered in the home, the question must be answered on its merits. From a rather large experience of ten years of home obstetrics, I must answer in the affirmative. Many times during these ten years mentioned I was called to see women in labor whom I had never seen before. If time permitted, I sent to my office or home for supplies; if it did not, it was possible to sterilize towels for draping the patient, prepare the patient, use rubber gloves and give an anesthetic. My own records show by comparison that women were equally as safe in the home as in the hospital. True, hospital conveniences and hospital privileges will be missed, yet it can be done. The only prophylactic measures that can be practiced are fundamentals; yet fundamentals are the same in the hospital, in the mansion, or in the hovel.

After graduation and internship, the state upon the completion of a satisfactory examination issues a certificate to practice medicine. The cost to the medical school for each graduate varies from \$800 to \$2,500 a year or \$3,200 to \$10,000 for the four years. The cost to the student varies from \$8,000 to \$15,000 for his academic and medical education, yet as we analyze his nine years of training, we find it is for only three or three and one-half years that doctors direct his training and that internships have little supervision other than those connected with teaching institutions. Yet they care for expectant mothers.

May I be pardoned for a suggestion that at present is Utopian in application? I intimated, from Dr. Hutchins' suggestion, that the first two years of college should be given in junior colleges and at home and that these hours be cultured hours. I would also suggest that the medical school authorities determine the fitness of students entering medicine by establishing a medical school campus where the future doctor will be taught or supervised by doctors and be associated with the teachers, staff members of the hospital, internes, medical students, and with all the organized agencies of medicine from the time he starts his pre-medical work.

Medicine is divided into two parts, the science of medicine and the art of medicine or people. In mentioning people I refer to their emotions and their problems. I refer to their emotions of love and hate, joy and sorrow, ambitions, hopes, and disappointments, to their problems whether they are physical, mental, economic, social, or spiritual. To know these develops a love for people, a sympathy for people and a desire to do for people. Service becomes the major thought, and it is then and only then that the science and art of medicine can be practiced effectively. Otherwise service is only for the loaves and fishes. I am firmly of the belief that our materialistic attitude has caused us to lose sight of a class of people who have been the backbone of every man's success. I am also convinced that when people are thought of and cared for as suggested, state medicine will be forgotten and our clinical services will be in a great proportion supplanted with profitable patients. I do not hesitate to say that whatever success I may have attained to date, the greatest influence that I have had and the most lasting friendships that I have enjoyed have been among this forgotten class, the so-called poor.

So far we have only discussed the inherited and environmental development of the physician or specialist. May we turn for a time to his activities as factors that influence obstetric improvement?

We believe that labor with few exceptions is a normal physiologic process. We further believe that the only difference between physiologic and pathologic obstetrics in many instances is that greatest of all trained obstetric virtues, the ability to wait. We believe that it takes trained, intelligent, reasoning fears and a fear for right to appreciate physio-

dare say most often with safety. Yet example, influence, writings, and discussion of these methods to or before other than this group or a similar group are directly harmful to the profession as a whole.

So much unwarranted space has recently been given to the subject of sedation that I hesitate to discuss it. Suffice to say that the success or failure of sedation rests with the scientific study and scientific application of the subject. We would urgently suggest that we as specialists do not put into print, discuss, or employ any means or method that has not first been proved to have, not only a scientific background, but a practical and safe application. The influence of the specialist is too far reaching to allow ourselves to influence or be influenced by any means or method that may be detrimental to any American mother.

It has been interesting to observe a hospital in my city that has been open to any member of the county Society. Ten thousand cases have been cared for by some 200 physicians. No physician has ever been denied the privilege of the hospital because of mistakes he may have made. From suggestion and assistance, mistakes have been remedied and individual obstetrics improved. It is most interesting that the statistics of this hospital have been a model for our other hospitals. I mention this hospital since the result has been attained through the efforts and influence of a member of this Society. I mention this record to show what a courageous fear for right, one person can create in any city, town, or community.

Some fifteen years ago a group in our city of which I was a member became interested in the induction of labor, or labor by appointment. Soon every medical society in western Missouri and eastern Kansas was deluged with papers. In time sufficient adverse data were gathered to restore reason, morbidity and mortality being the restorative agents. Thus, we have seen to our sorrow the dangers and folly of such teaching and practices. Even in the last year I have been quoted as advocating such a procedure. Surely "the evil that men do, lives after them."

I mention this experience to emphasize how lasting an influence papers, discussions, and demonstration may have on the profession as a whole and also to emphasize the fact that physicians with little or no training will attempt any method or procedure and justify their acts or procedure from papers or discussions of the specialist.

Another problem that mocks us and plagues us is the abortion situation. Dr. Litzenberg in his presidential address before the American Association of Obstetricians, Gynecologists and Abdominal Surgeons pointed out the dangers of our rapidly falling birth rate. From comparing our situation with the history of Rome and other great nations of the past he said, "We would soon face a national decay if our birth rate continued to fall as it is doing."

Dr. Fred Taussig has estimated that there are 700,000 abortions in the United States yearly with a loss of 10,000 women. Dr. Taussig does

Our conception of right and wrong and our appreciation of service to people determine the safety of our application of fundamentals in the home or in the hospital.

It is also a fact that the majority of women in the United States are delivered by the general practitioner. Most often in discussing maternal welfare problems the general practitioner is given first place in our criticisms. This thought is worthy of serious consideration. That fundamental training in our schools has been the best, no one can deny. It is well to ask, Where did he interne? Who taught him that all these routines, selective operations and prophylactic procedures are fundamental and safe? Not our schools, but specialists, you and I taught him through the literature, through example, and through influence. Without question, this is a swamp that must be drained and reclaimed by the specialist.

I recall that in going from home obstetrics to hospital obstetrics I was influenced by specialists, older men, busy men and successful men and my patients were told by others in the hospital of all these prophylactic measures. Formerly in the home I had determined that patients could have their babies and upon my assurance, they expected that only time was necessary for delivery. My courageous fears gave way to competitive and economic fears and needless to say my results suffered until such a time as reason again supplanted fear. I mention these experiences since several of the younger men of this group have told me similar experiences. Our only measure of success must be by the yardstick of the well woman.

From almost every land where maternal welfare problems are being studied, the reports, with few exceptions, are that interference is our greatest factor in the loss of mothers and children. Yet there is a fundamental known to every nation where obstetrics is taught: that interference is to be done only in the interest of the mother or the baby. Quite old-fashioned, seemingly senile in its application, yet it is and always will be practical since it is right. Present-day trend seems to say this is a teaching for students but not for specialists. As has been intimated there have crept into our obstetric literature certain terms that are most alluring but dangerous, namely: Prophylactic measures, selective measures, routine measures, and measures for shortening or terminating labor. Probably at times all have been lulled to sleep by these time-saving measures only to find with the dawn of results not the well woman but the woman showing for days, months, or a lifetime the stigma of a procedure. It is now time to acknowledge that these procedures save the time only of the profession and that they should have a very limited place in the scientific and practical life of our obstetric family.

It must be granted that this group, because of their training, judgment and experience, can do all types of interference with skill and I

plague or epidemic yet known. The more so since it not only involves the populating of our nation but the decay of our nation, mentally, physically, and spiritually.

Too much encouragement cannot be given to the intensive study and investigation of accidental abortions in view of the efficient results already reported. A 13 per cent mortality in therapeutic abortions as reported from the Children's Bureau is scientifically too high. I am of the belief that too much emphasis is given to the subject in the literature, not so much by those whose fears for the right are so well known, but by those whose fears of wrong seem to be lost in the quest for gold. Unfortunately these use their interpretation of the literature as a smoke screen to hide their death-dealing practice, and this screen may hide causes involved in the 13 per cent mortality of so-called therapeutic abortions.

Such a plague requires strict quarantine. No better prophylactic or preventive measure could be instituted than the cooperation of medical agencies with law-enforcing agencies.

Two types of infected areas are found. First, those of the profession without organized medicine. As we have observed, these are the *Anopheles* type that are filling up our clinical services. Only the oil of law-enforcing agencies can destroy their breeding places. The second group belong to organized medicine. These should receive the same treatment offered through law-enforcing agencies. Besides this, a preventive measure would be professional ostracism. The popularity of these is due to their professional standing and the safety for social inconveniences found in the hospitals that admit this group without questioning their procedures. This group preys on the intelligentsia group and teach them their modern term of social inconveniences. This group of people are of importance since they so thoroughly represent the truly American stock and are the ones who should have children. Aside from mental and physical qualification they are amply able to provide for children. As we observe the decreasing number of children in such families, we cannot refrain from asking, Is childbearing and the responsibility of caring for children quite as much a sociologic factor in the happiness of the home as those problems associated with idleness in the home?

Like all plagues and epidemics the success of quarantine and prevention depends upon the cooperation of the individual physician and specialist. The treatment to be applied by the individual physician or specialist is best expressed by a colleague of mine, Dr. Calkins, who said, "Cool and considerate reasoning must supplant social and economic dictation and weak-kneed accession to the importation of influential patients."

In the discussion of obstetric fears, I trust I may be pardoned for sentimental flights. However, this Society's chief purpose in organiza-

not attempt to estimate the morbidity in these cases, the loss of blood, women with infections that get well, necessary and unnecessary operations and invalidism, that are so well known to each of us, and deaths that are indirectly caused from an abortion. Such a situation with such a mortality and such a morbidity is an obstetric plague. Such a record of smallpox, yellow fever, diphtheria, or typhoid fever would cause the state and national medical agencies to act at once. Contagious diseases have all been lessened in frequency or eliminated through efforts of the profession. Millions of dollars have been spent and many valuable lives sacrificed to eliminate disease that involves life. Yet it is a serious question as to whether or not the profession is directly or indirectly responsible for this obstetric plague.

We are faced with three problems:

First: Those accidental abortions that may be avoided by better prenatal care and a more intense study of the causes of accidental abortions. As we know, much progress is being made in this field.

Second: The therapeutic abortion! I refer to those done with the hope of conserving the lives and health of women. Dr. Adair quotes the child welfare bureau as stating that there is a 13 per cent mortality in therapeutic abortions. Such a statement causes us to ask seriously if it would not be better for the obstetricians to cooperate more with the specialists in the indicated lines of medicine in order that this 13 per cent mortality may be reduced to a minimum. With the exception of toxemias and nephritis most of the other serious indications have largely been superseded by improved medical treatment.

Third: The criminal abortion whether self- or medically produced and coming to us secondarily is a difficult and serious problem to the younger men and to many of the older members of our specialty. If the patient is a clinic patient it is well to care for her as seems best on our various clinical services. However, the cooperation of medical agencies with law agencies will reduce the excessive numbers we are caring for. In private practice there can be only one stand, that the patient go into a hospital and before witnesses write or sign a statement as to who did the abortion and how it was done. This relieves the reputable obstetrician and hospital of all criminal responsibility. The signed statement is then to be made a part of the hospital record. The speaker has followed this routine for several years with perfect satisfaction to himself and I also know that this plan is followed successfully by many others of our specialty. I would further advocate that all abortions from whatever cause should have a separate certificate or report that must be a part of our health agencies' record.

The destruction of 700,000 defenseless lives yearly and 10,000 known mothers is an obstetric plague, more revolting in its aspect than any

THE SURGICAL TREATMENT OF COMPLETE PERINEAL TEARS IN THE FEMALE*

NORMAN F. MILLER, M.D., AND WILLIS BROWN, M.D., ANN ARBOR, MICH.
(From the Department of Obstetrics and Gynecology, University of Michigan)

RELUCTANTLY indeed does the cold gray past reveal its secrets. From its silent depths come only patchy fragments, telltale evidences, from which we may construct our concept of remote gynecology. Since earliest times, tearing of the rectum at the time of parturition has been looked upon as a most depressing accident—saddening to the patient, despairing to the physician, and always necessitating a gloomy prognosis. Cure depended on the generosity of nature, on binding the legs together and on such other traditional remedies as existed at the time. Indeed this appears to have been the prevailing method of treatment for centuries, and it continued long after surgical union had first been tried.

As late as 1840 Payan recommended confinement to bed for six weeks, the patient to be kept on her side and her legs tied together. In 1864 Robinson advocated similar treatment, but was less emphatic as to its efficacy, merely suggesting that it be tried before operation was undertaken. These probably represent late and more or less isolated uses of posture treatment. Guillemeau, a student and contemporary of Ambroise Paré (1510-1590), was probably the first to attempt surgical union of a completely ruptured perineum. Later, Mauriceau (1637-1709) and Smellie (1697-1763) recommended operation and suturing, but there is no evidence to show that they ever performed restoration by this method. General acceptance of suturing was inevitable but slow. Saucerotte's notable contribution appeared in 1798, and Mentzel described a button suture for this purpose during the same year, Figs. 1 to 7. In 1801 Nedel told of freshening and approximating the edges. He also recommended fat and oil applications with soft massaging to make the perineum more yielding and less likely to tear. That operation was still something of a last resort is suggested by Wendelstadt's description of a case which he treated in 1803. The wound was cleansed and the legs were tied together, but due to exhaustion from sleeplessness and constant irritation from diarrhea, the legs had to be loosened and this form of treatment given up. Later the edges of the wound were pared and approximated with strong wax thread.

Notwithstanding the fact that surgical correction was known it was not until half a century later that reports of surgical cures commenced to occupy a conspicuous place in medical literature. Among the many prominent names of this era we find Jobert, Tragher, Maisonneuve, Verhaeghe, Tanner, and Laugier. With surgical treatment so generally accepted we pick up new threads emanating from scientific discoveries

*Read at the Eighth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Detroit, Mich., October 15 to 17, 1936.

tion was for the improvement of obstetries in this area. Our beginning was the individual physician or specialist and our objective the life and health of the mothers and their offsprings. We have advocated that this is a moral problem as well as a scientific problem. Therefore, sentiment cannot be eliminated as the ruling emotion in its solution. No one can question the motives of the sponsors of this Society, representing as they have the parent organizations, the American Gynecological Society and the American Association of Obstetricians, Gynecologists and Abdominal Surgeons. No one can question the efficiency of this organization nor its previous leadership. The function of the Society and the manner in which it solves its problems will, however, determine its success.

Each state in this area may have a well-organized and well-functioning maternal welfare committee. Every member of this Society may be certified by our American Board as a specialist in our specialty, yet in the last analysis the problem becomes the relation of the individual physician or specialist to the individual expectant mother.

In my humble opinion a trained, an intelligent, a reasoning, a courageous fear, and a fear of right must be the qualifications of the individual physician or specialist caring for women during the prenatal, natal, and postnatal periods.

Is it asking too much, is it stating the situation too emphatically, to say the problem is ours as specialists? That as specialists we are the liaison between the school and the general profession? Is our philosophy entirely wrong when we say that obstetric fears are largely responsible for our standing among the nations in maternal morbidity and mortality? Again is our philosophy of obstetric fears entirely wrong when we advocate that obstetric fear is an inherited or acquired conception of right and wrong based on the teaching of the Great Physician?

1107 BRYANT BUILDING

Buchner, E. F., Jr.: The Rate of Growth Before Birth, J. Tenn. M. A. 29: 131, 1936.

Plotting the averages of all available curves of anatomic and radiographic measurements on the same coordinates, together with the curve of the probability of survival, as derived for want of authoritative figures from the generally accepted clinical impression, resulted in a graph of considerable practical value in obstetrics and pediatrics. Allowing for errors in draftsmanship both the length and weight do not increase as smooth curves, and anatomic and radiographic measurements of the head parallel each other fairly closely.

It is suggested that this graph, together with immediate length and weight measurements of the newborn child, may help in the quick and more accurate determination of the stage of its development.

J. P. GREENHILL.

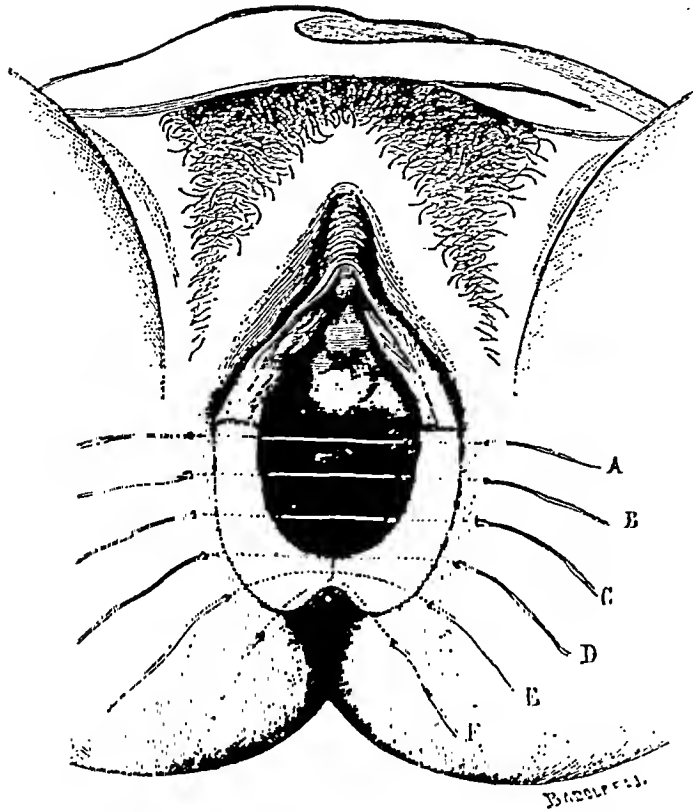


Fig. 2.—Technique of perineal repair about 1870. (From Arch. de Tocologie, 1876.)

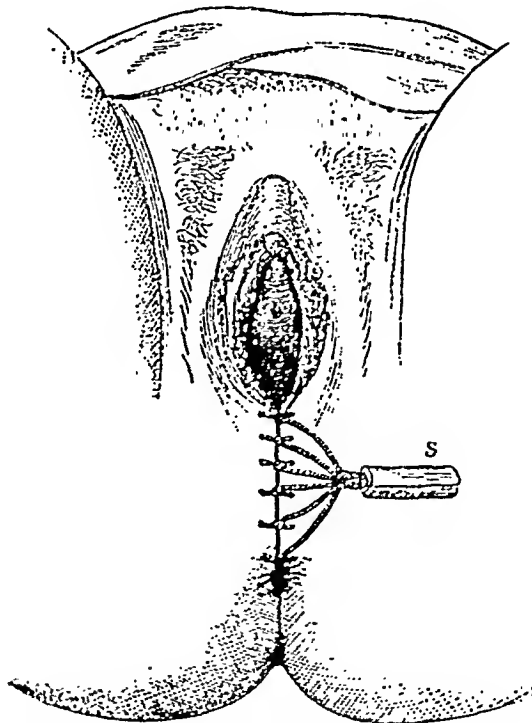


Fig. 3.—Technique of perineal repair about 1870. (From Arch. de Tocologie, 1876.)

of the times. The use of chloroform is mentioned and more attention is given to anatomic restoration of the perineal body and to special technical improvements. Since the need for avoiding tension was recognized even before the application of suturing, it is hardly to be expected that this fundamental principle should be discarded with the acceptance of surgical restoration. Tying the legs together was still used in conjunction with suturing. As refinements in technique continued, we find many incidental controversies arising. The matter of diet and postoperative care of the bowel became a matter of con-

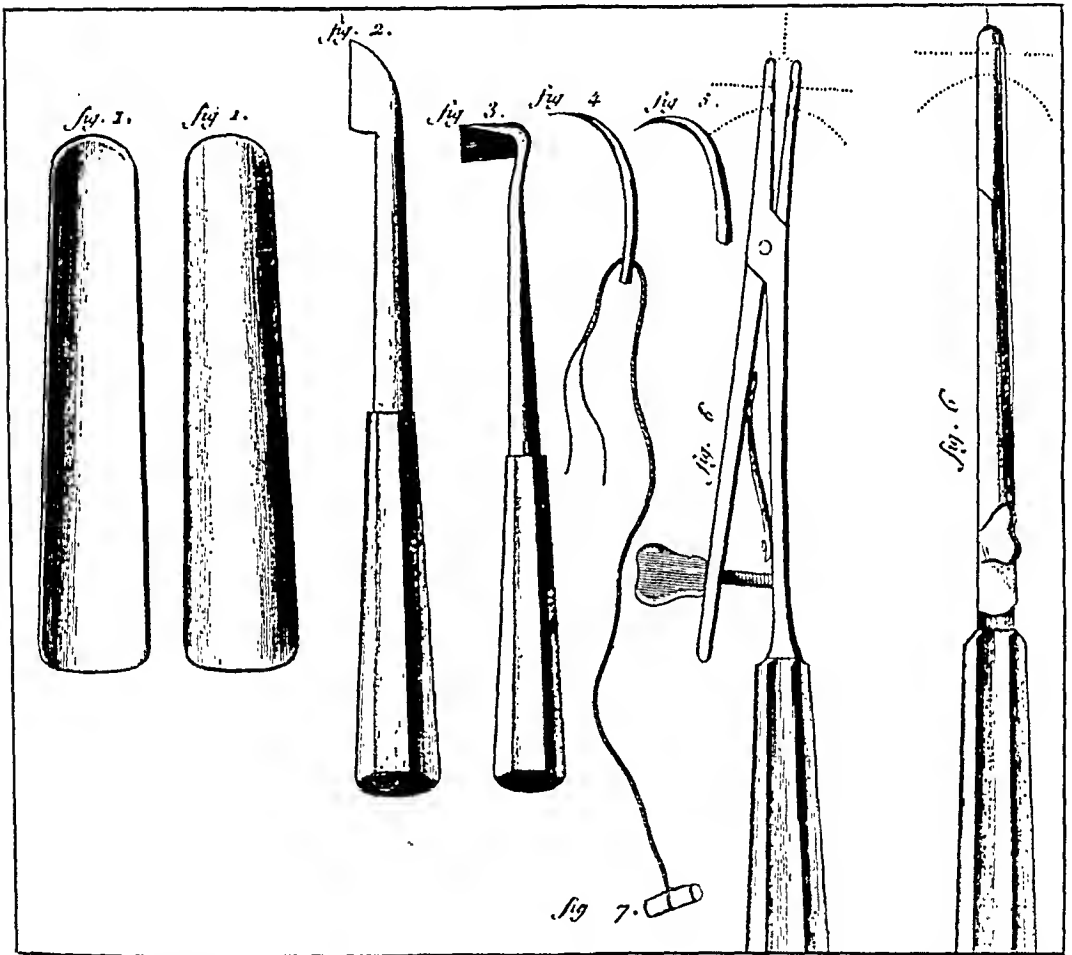


Fig. 1.—Instruments devised by Saucerotte for use in the repair of complete tears of the perineum (1798).

tention; there was about an even division for and against the use of opium following operation. Now, too, we see the ancient quill losing favor, Hicks and Bryant in 1862 being among the first to discard it for the ordinary suture. It is with regret indeed that we must pass rapidly through this notable era, the historian's paradise.

Most noteworthy, perhaps, among the contributions of the last half of the nineteenth century were those of I. Baker Brown and our distinguished D. H. Agnew (1868) and J. C. Warren (1882) whose meritorious contributions will long be treasured.

operation combined with subcutaneous cutting of the sphincter. This latter step explains our term *paradoxical operation*. Preoperative preparation and postoperative care generally applied to Group II cases (those repaired by paradoxical method) may be outlined as follows:

Preoperative: (1) One ounce of castor oil daily for three days prior to operation. (2) Soapsuds enema on day prior to and morning of operation. Repeated until return is clear. (3) Low residue diet commencing three days before operation, and clear liquids only on day before operation.

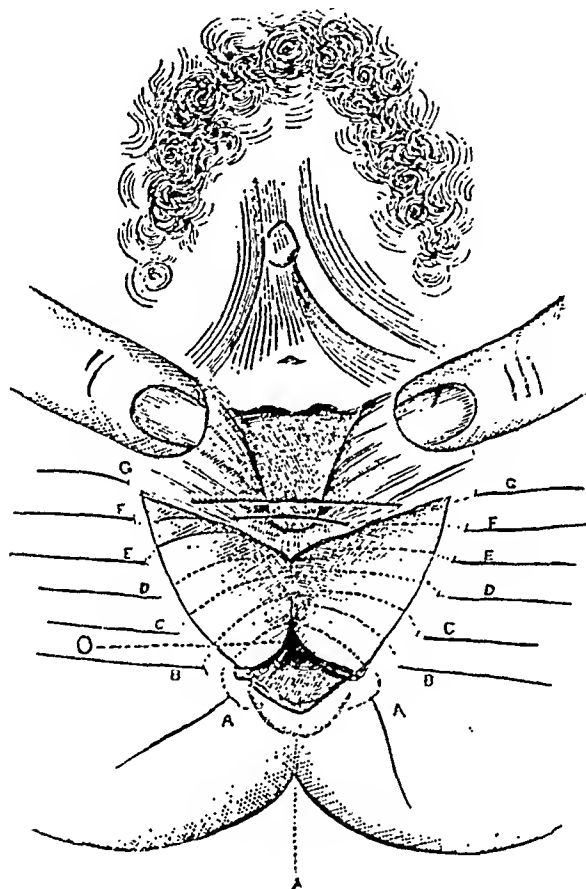


Fig. 5.—Repair of complete laceration. (H. T. Hanks, The Medical Record, 1882.)

Postoperative: (1) Clear liquids for nine days. (2) Any liquids on tenth day and soft diet on the eleventh. (3) One teaspoonful of paregoric four times daily for first nine days. (4) Retention oil enema daily commencing tenth day after operation. (5) One ounce of castor oil by mouth on twelfth day.

Our preoperative preparation of patients with third-degree tears may appear unnecessarily elaborate. It represents an effort to minimize the danger of infection and to make the patient comfortable. By thorough evacuation of the bowel, there is less likelihood of contamination, and peristalsis during convalescence is reduced. The need for tying up the bowel postoperatively is not unanimously agreed to in the literature and may well deserve further study.

Ristine, Noble and Kelly inaugurated twentieth century practice with modifications of the flap operation, a procedure which today continues to be among the most satisfactory methods for repair. By then, however, the pendulum had reached the center of its arc, for interest in this subject seemed to fall off. An occasional revival of the subject is found in the reports of Hall, III, Hamner, Goldspoon, Phaneuf, Smith and Linton, and Royston.

Our own study is based on 182 chronic complete tears treated at the University of Michigan Hospital. No acute tears are included. The cases studied are divided into two groups, i.e., those operated upon by various methods prior to 1931, comprising 144 cases (Group I); and 38 patients operated upon since 1931 by what we speak of as

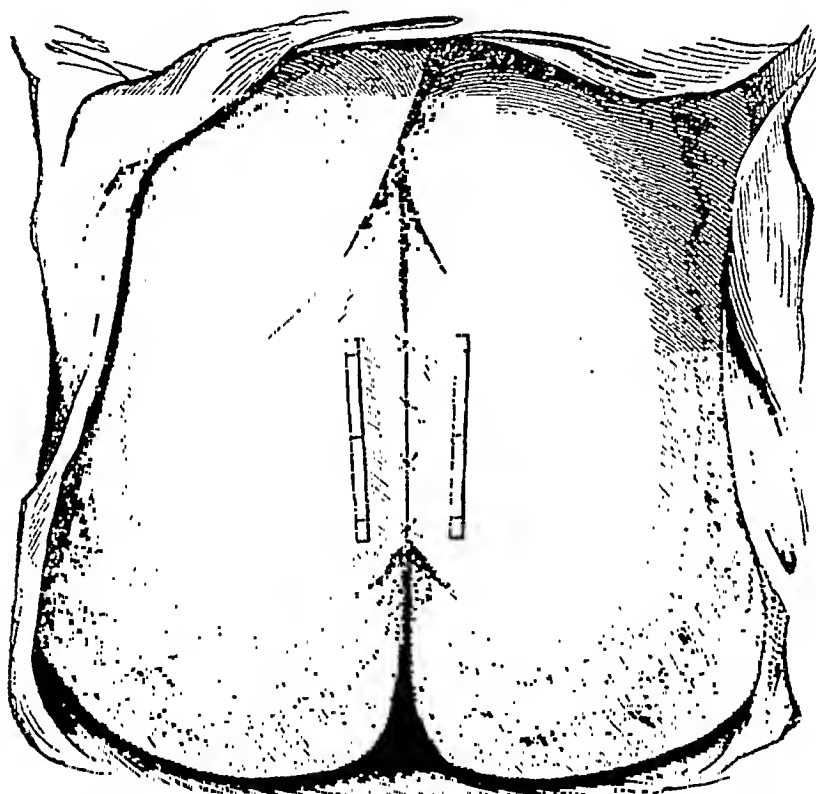


Fig. 4.—Perineal closure advocated by J. T. Bradford. (Cincin. Lancet and Obst., 1869.)

the *paradoxical operation* (Group II). The operative techniques used in the cases of Group I are difficult to name because of their general similarity but included those in vogue during the early years of the twentieth century (1901-1931). At first what was known as the Emmett operation was preferred; that gradually gave way to the flap technique described by Warren (1882), Ristine (1900), and in 1902, by Noble. Minor variations were common but basically the above procedures were used for the thirty-year period, providing the Group I cases. Since July 1, 1931, all third-degree tears (Group II) which we have treated have been repaired by what is fundamentally the flap

as a preliminary operation. Of real significance in this connection is the fact that each unsuccessful attempt at repair leads to more scarring and lessens the chances for success in later attempts, a fact to be borne in mind by every physician who contemplates the repair of a third-degree tear.

Since the operative site in every complete tear is always potentially infected, painstaking precautions to avoid excessive contamination are always wise. It is here, perhaps, that the flap technique is of greatest value. Not only does the flap adequately provide for the

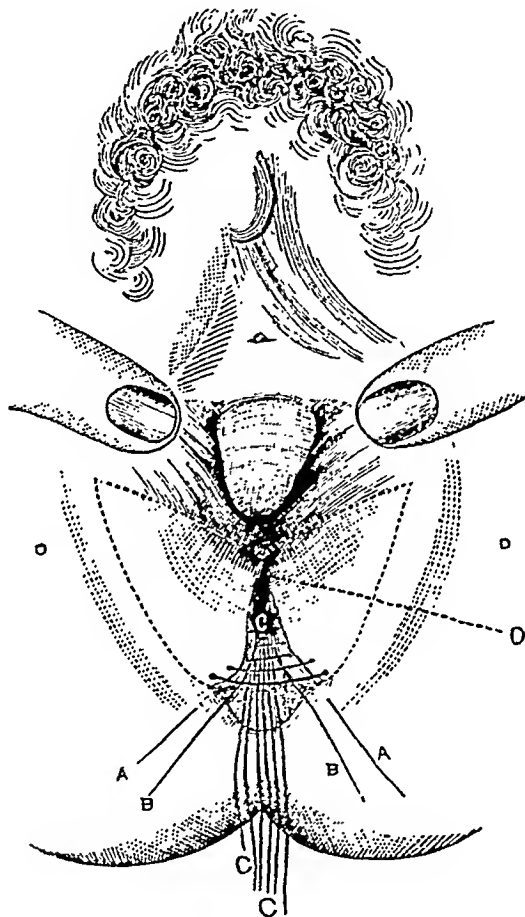


Fig. 7.—Repair of complete laceration. (*H. T. Hanks, The Medical Record, 1882.*)

deficit in the anterior rectal wall in most cases but in addition it forms an intact protective barrier against contamination of the operative field. Any redundant or excessive mucous membrane may be excised during the final steps of the operation. It is because it more nearly fulfills the second demand of sound plastic surgery that we prefer the flap technique.

The importance of relieving tension was apparently well recognized by the earliest operators. Noteworthy early attempts to minimize tension are seen in the tying together of the legs and in Dieffen-

The steps of the paradoxical operation are shown in Figs. 8 to 14. Locating the sphincter ends, particularly in old cases, is facilitated by digital palpation of the sphincter through the anus when exploring with a blunt curved hemostat as shown in Fig. 14.

Since tension is to be released by cutting the sphincter, only two No. 1 chromic stitches are used for approximating the muscle ends. Cutting the sphincter directly posterior does not appear to relieve tension sufficiently because of the close intermingling and attachment of the posterior levator ani muscle fibers converging toward their coccygeal

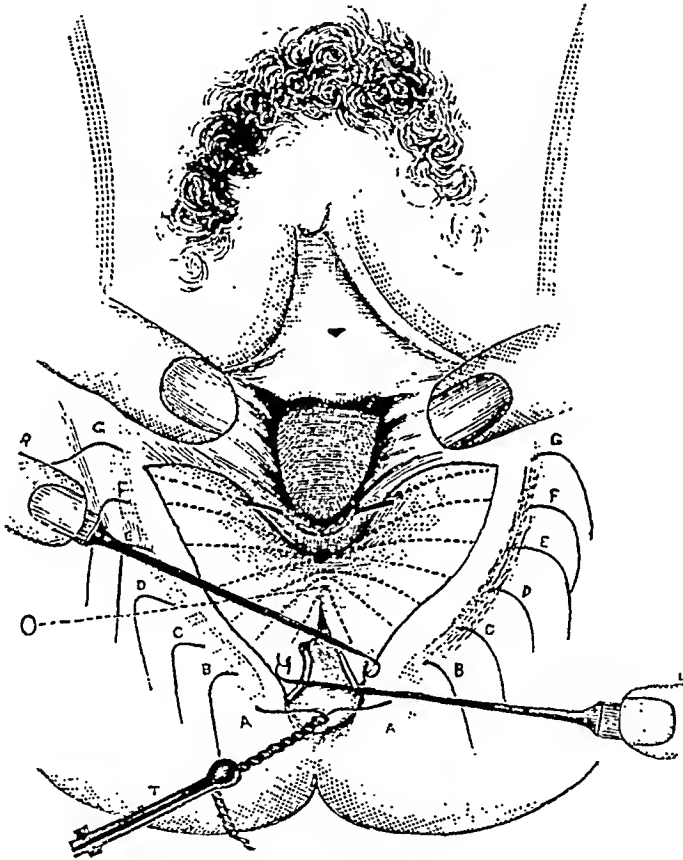


Fig. 6.—Repair of complete laceration. (H. T. Hanks, *The Medical Record*, 1882.)

attachment. In long standing cases, the sphincter may be cut as the initial step, thereby facilitating approximation of the anterior sphincter ends.

At least three fundamental principles are essential to successful plastic surgery; namely, (1) good blood supply, (2) absence of infection, and (3) avoidance of tension. The first fundamental, good blood supply, scarcely need be commented upon. Probably no one technique or procedure is very much better than another in this respect, yet adequate blood supply is extremely important and is fortunately present in the perineum, except in badly scarred, often-operated cases. Excessive cicatrix may often be excised or incised if necessary

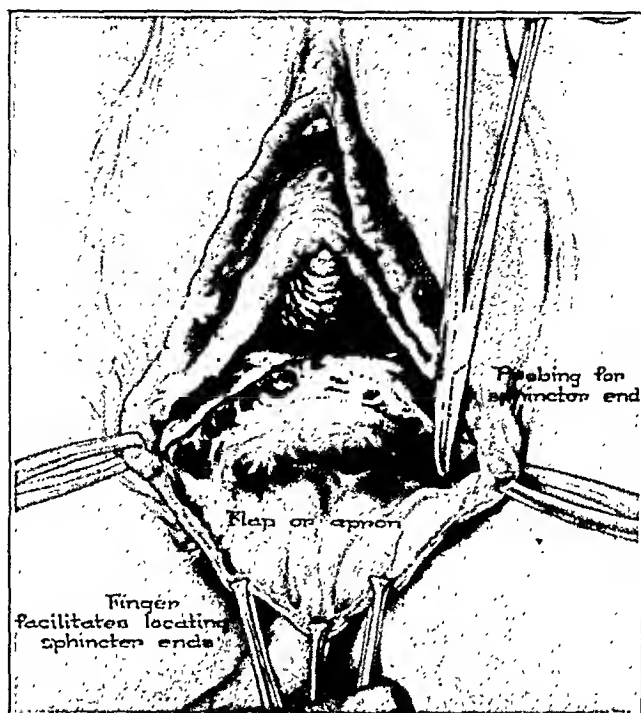


Fig. 10.—Probing for the sphincter end. Note how flap or apron tends to protect operative field. In the majority of cases the flap also adequately provides for the deficit in the anterior rectal wall.

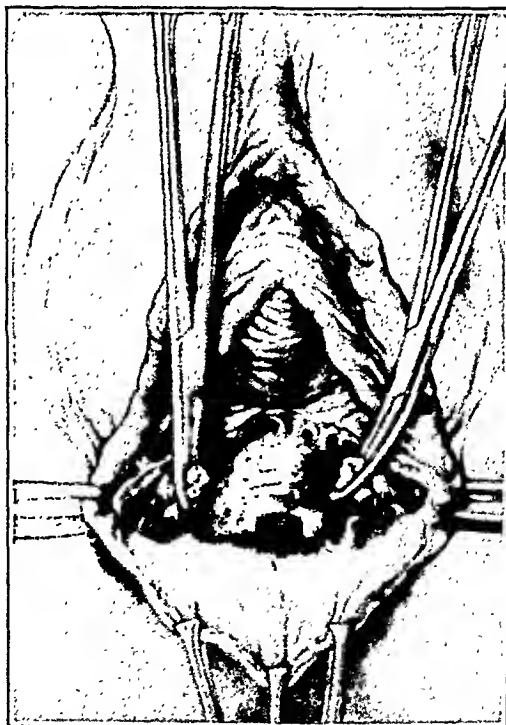


Fig. 11.—In about one-half of the cases the sphincter ends are readily isolated. In others it is necessary to take adjacent levator fibers.

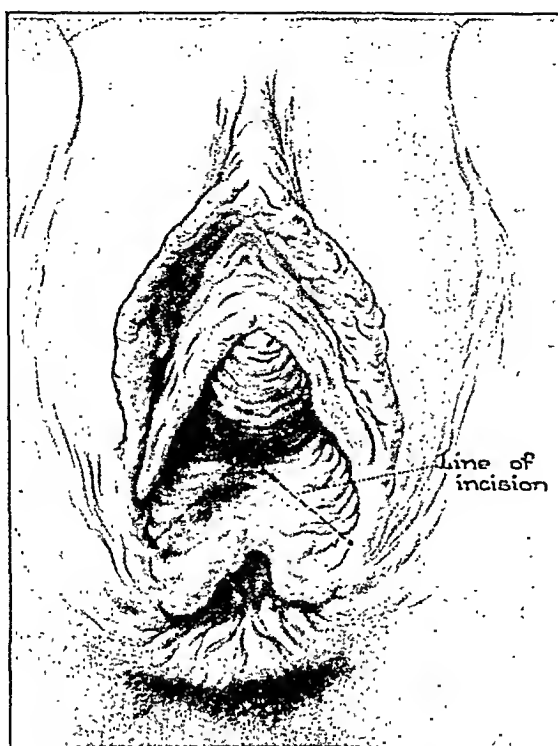


Fig. 8.—Showing line of incision for developing flap.

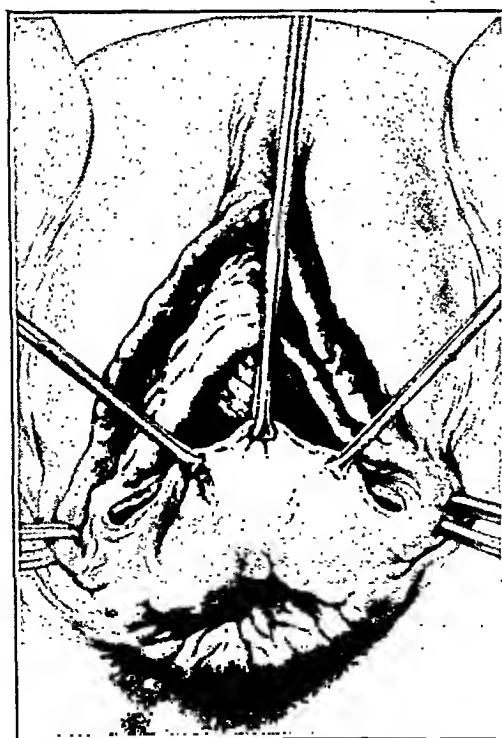


Fig. 9.—Dissection of flap completed.

bach's incisions. When first we cut the sphincter for release of tension, we thought it might be original but extensive study of the literature revealed that this was a very old and well-proved procedure.

Imagine, if you can, an operating setup half a century before the world knew of Pasteur and infection, seventy-five years before the illustrious Lister and antisepsis, decades before the discovery of chloroform. Take away the surgical knowledge acquired in the past 150 years, and we have the situation faced by the stern but courageous Saucerotte and his able assistants, Castara and Rousel. It was no mean problem that caused them concern that day in the year 1798. Their patient, now forty days postpartum, demanded something be done for the unbearable fecal incontinence. Posture and other traditional remedies had proved valueless. A first fruitless attempt with the then almost unheard-of suture method had failed. Impelled by the undaunted spirit of their patient, these courageous pioneers again undertook repair, but this time at the suggestion of one of the assistants the sphincter was cut in order to release tension. There followed days of anxious waiting, needless as it proved, for their patient was cured. But Saucerotte and his assistants were far ahead of their time and the real value of their contribution did not become known until popularized by such illustrious men as I. Baker Brown, Chassaignac, Hugnier, Mereier, and Velpeau. The principle of release of tension was generally recognized but severing the sphincter was by no means the only accepted method. Some preferred the semilunar incisions of Jobert and Dieffenbach, others the tension suture. While Brown's astonishing results in 75 cases reported in 1860 must be looked upon as the work of a remarkably skillful operator, Brown himself attributed much of his success to his practice of cutting the sphincter.

Comparison of results obtained by various operative techniques is complicated by the fact that there appears to be no generally accepted criteria or standard of cure. As the terms used in describing the results are often relative, it is difficult to know just how good a "satisfactory result" really may be. There is need for a better grading of results, and for general acceptance of such grading. Another factor in determining the value of any one method is the end or late result of operation. One does not always achieve nor should one expect immediate and perfect functioning from a sphincter which has remained functionless for many years. Consequently, follow-up examinations might well show a higher degree of success than reports based on immediate postoperative evidence.

We are opposed to the use of such terms as "cured," "excellent," or "good," because these terms permit wide range of interpretation. In this study the term *function restored* is applied to all cases where control over the fecal stream is regained. In some cases of this group

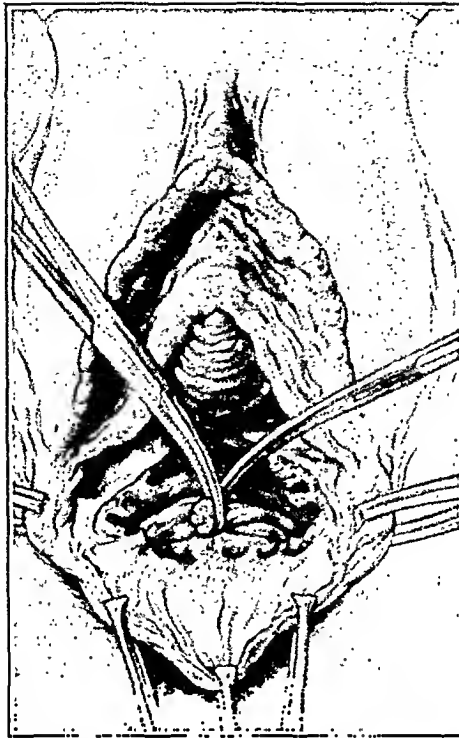


Fig. 12.—Approximation of the sphincter ends may be facilitated by early cutting of the sphincter.

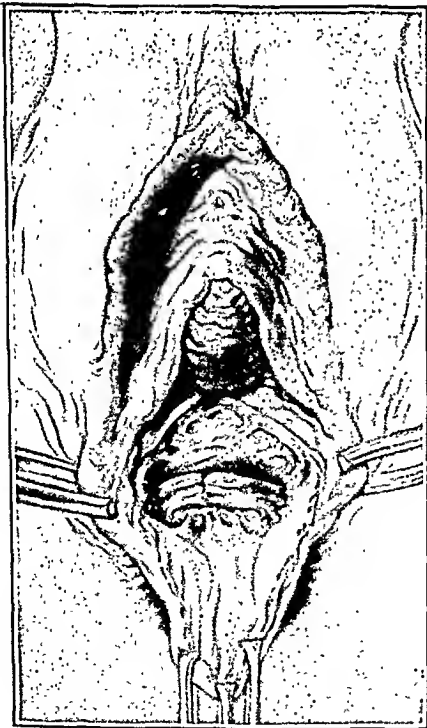


Fig. 13.

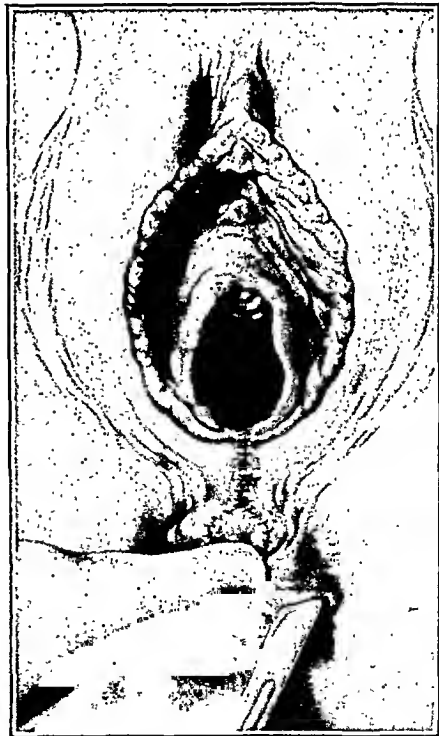


Fig. 14.

Fig. 13.—Since there remains little tension on the anteriorly united sphincter, only two chromic No. 1 sutures are used to keep the ends in apposition.

Fig. 14.—In the average case the operation is completed by subcutaneous cutting of the sphincter in the posterior quadrant.

TABLE III. NUMBER OF OPERATIONS PRIOR TO ADMITTANCE

NO. OF OPERATIONS	GROUP I*	GROUP II†
I	55	18
II	8	4
III	2	1
IV	0	0
V	2	0
VI	0	1

*The 67 patients in Group I operated upon once or more prior to admittance averaged 1.3 operations per patient.

†Twenty-four of the 38 patients finally treated by paradoxical methods averaged 1.5 operations per patient prior to admittance.

the perineum. Complete cure and perfect control occur as the result of an intact sphincter but many patients seem to do remarkably well once their levators become properly trained and adequately developed.

Results obtained in our series of 182 cases are shown in Table IV.

TABLE IV. RESULTS

	GROUP I	GROUP II
Function restored	71.00%	87.00%
Function improved	15.00	8.00
Failure	10.00	5.00
Unknown	5.00	0.00

We attribute the higher incidence of cures in Group II (paradoxical repairs) to the release of tension on the anteriorly united sphincter.

Unfortunately a general comparison of results is not possible. There is a noticeable lack of recorded results in the literature and, as previously stated, those which do appear fail to make a decisive grading. Definite commitment concerning results obtained is essential if we are to make healthy comparisons with the hope of ultimately being able to arrive at the most desirable method of repair.

SUMMARY

1. Historic highlights in the treatment of third-degree tears are revealed.

2. Surgical principles pertinent to the correction of third-degree lacerations are discussed.

3. Data on the results of treatment in 182 patients are presented.

4. The need for a universal standard in appraising results of treatment is pointed out and certain criteria and terminology are suggested.

5. The *paradoxical repair* (flap operation plus sphincter cutting) is illustrated.

6. It is hoped that results following other methods of operative correction will be reported in order that we may ultimately determine the most satisfactory method of repair.

7. An extensive bibliography is appended.

the control over gas was not entirely satisfactory, but sphincteric action was restored. So-called *perfect* results are common following repair of fresh complete tears, but in old and long-standing cases, we believe that examination two weeks postoperative does not always show sufficient return of sphincter activity to permit of complete control of gas. By *function improved* we mean control over solid or normal stools but imperfect or no control of gas or liquid stools. *Failure* of course means no control whatsoever, even though the perineum may appear well reconstructed. The *unknown* results applied to 5 per cent of Group I cases occurred early in the series and no results were recorded in the history. These may have been failures but for lack of evidence it appears wiser to classify the result as unknown. We believe the terms used to designate result and the criteria upon which they are based are reasonable, and we suggest their use in future reports.

Questionnaire follow-up was attempted in this series but was unsatisfactory. The number of replies from early cases were too few to be of value. Our data then are based on results noted at the time of discharge from the hospital. If improvement does occur weeks after operation in old chronic cases, then we may reasonably assume a higher incidence of cures, especially in those treated by the paradoxical operation. Many of our patients had suffered fecal incontinence for fifteen years or more, the longest being thirty-three years. The average duration of the tear was nine years.

TABLE I. GENERAL DATA

Average age of patients	33 years
Average duration of tear	9 years
Average parity	3.4 per cent

TABLE II. ETIOLOGY

	NUMBER	PER CENT
Nonoperative delivery	46	25.00
Operative delivery	126	69.00
Surgery	7	4.00
Etiology unknown	3	2.00
	182	100.00

In discussing results one cannot overlook the fact that previous unsuccessful operation with incidental scarring increases the technical difficulties and reduces the prognosis for return of function. Note that 40 per cent of Group I, and 63 per cent of Group II cases had undergone operation one to six times prior to admittance to the University Hospital (Table III).

Furthermore, we believe that in any evaluation of results due credit must be given the levator ani muscles which are utilized in building up

SIX NORMAL AND COMPLETE PRESOMITE HUMAN OVA*

JOHN I. BREWER, M.D., PH.D., AND JAMES E. FITZGERALD, M.D.,
CHICAGO, ILL.

(From the Department of Obstetrics and Gynecology and the Henry Baird Favill Laboratory of St. Luke's Hospital, and the Department of Obstetrics and Gynecology of Northwestern University Medical School)

THE possession of six perfectly preserved, stained, and serially sectioned presomite human ova of different ages in one laboratory affords excellent material for detailed study of implantation, early placentation, and embryonic development. There are approximately 75 presomite human ova reported in the world literature. The majority, however, are of little value. Only 30 have sufficient data and are normal enough to permit the drawing of conclusions. Only a few are anatomically complete and sectioned favorably. Interpretation of the findings have been reported by such a diversified group of workers that uniformity is lacking. To obviate this, Grosser, Streeter, Teacher, Bryce, Florian and Hill, and others have made collective studies of all the presomite ova to which they have had access.

Our group comprises six presomite ova, all of which were obtained by hysterectomy. In none was there any abnormality of the pregnancy. This is important in considering the actual stage of development. All were fixed within ten minutes after clamping the uterine blood supply. Each was sectioned and arranged serially. Four were oriented so that the embryonic disc was cut in cross-section and two were cut sagittally. There were no sections lost in any of the specimens. Various fixing solutions and stains were used. One ovum, the Jones-Brewer I, is the youngest human ovum to have cytologic methods applied to placentation. The Edwards-Jones-Brewer specimen is the youngest normal and anatomically complete ovum to be reported in the United States.

The latter is particularly adapted to a study of implantation because all sections include the entire thickness of the endometrium and a portion of myometrium. This makes possible a complete study of the vascular phenomena. Trophoblastic activity is equally well investigated in this ovum and the next youngest of our group, the Jones-Brewer I ovum.

VASCULAR PHENOMENA

The vascular changes in the endometrium of early pregnancies are identical to those phenomena in the normal menstrual cycle (Brewer).

*The Prize Award paper, read at the Eighth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Detroit, Mich., October 15 to 17, 1936. Aided by a grant from Mrs. Emmons Blaine and from the Rockefeller Institute to the University of Chicago.

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Yeast-like organisms isolated from vulvovaginitis and oral thrush were run through the fermentation tests and allowed to grow on Sabouraud's dextrose agar plates for observation of morphology. Those organisms failing to produce mycelium were called eryptococcus and those produueing mycelium, monilia.

Classifications of these organisms were made by correlation of fermentation and morphology. Fermentation groups were determined in 8 eryptococcus and 73 monilia strains isolated from vulvovaginitis of adults and oral thrush of infants.



Fig. 1.—The Edwards-Jones-Brewer ovum. This photomicrograph demonstrates the phenomenon of vasoconstriction. The spiral artery near the penetration zone has divided into two branches that extend parallel to one another. They are seen near their origin. One is dilated and filled with blood while the other is constricted near its origin and is empty. Such findings are frequent.

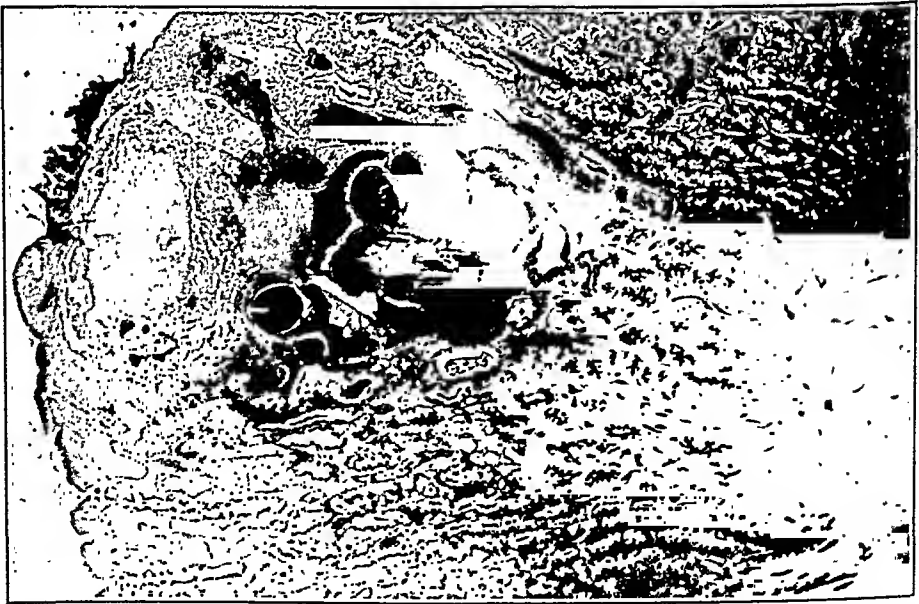


Fig. 2.—The Edwards-Jones-Brewer ovum. The photomicrograph shows the blastocyst embedded superficially in the decidua. The embryonic anlage is located at the most dependent pole. The surface coagulum is torn in part. About the blastocyst there are numerous dilated venous sinuses. There is a large basal sinus filled with blood which is connected to the large lateral sinuses. The basal glands are in many instances filled with blood.

The endometrial glands are the typical glands of pregnancy. Spiral arteries are traced to the endometrial surface except in the region of the blastocyst.

The myometrium contains a large spiral artery near its origin. It is located directly beneath the implantation site and accounts in part for the extensive hemorrhage noted in this specimen.

The changes in the endometrium in various phases of the normal cycle have been described recently by Bartelmez, Markee, Daron, and others. As Bartelmez points out, the essential characteristics of menstruation are extravasation of blood and necrosis of the superficial zone. Lahm in 1926 had already demonstrated constriction in the long spiral arteries with a resultant superficial necrosis of the endometrium. Meyer-Rügge and Markee substantiated these findings. Markee's work, based on observation in endometrial transplants in the anterior chamber of the eye in monkeys, conclusively proved the occurrence of vasoconstriction. The blanching phase dependent on vasoconstriction was increased markedly as the time of menstruation approached. The vasoconstriction with consequent ischemia lasting twelve hours or longer, he states, is sufficient to produce extravasation of blood and necrosis. The extravasation is usually quite superficial. Substantial evidence of vasoconstriction during the bleeding phase of menstruation was presented by Bartelmez. In his specimens he observed and pictured spiral arteries with open lumina projecting into the uterine cavity without hemorrhage about them and without blood in their lumina. These facts explain the means by which the bleeding at menstruation is controlled. It has been shown by Daron that the basal portion of the endometrium and the more peripheral portion are supplied by two distinctly separate types of arteries. His conclusions were based upon the fact that the arteries supplying the basal portion of the endometrium were less coiled and did not present the phenomena of vasoconstriction. The spiral arteries extending to the surface of the endometrium, he found, did undergo vasoconstriction.

The vascular changes in the endometrium during its cycle are not for the purpose of producing changes incident to menstruation, but rather are a preparation of a site for the implantation of the human ovum. This was suggested by Brewer in his observation on the Edwards-Jones-Brewer ovum. He showed that vasoconstriction of the long spiral arteries was frequent in the region of the implanted ovum. (Fig. 1.) The superficial portion of the arterial and venous systems was frequently congested in association with vasoconstriction of the basal portions. The extravasation of blood is found only superficially (Fig. 2).

The large amount of blood in the Edwards-Jones-Brewer ovum could be accounted for if one assumes that the patient was operated upon during or immediately following a period of blush (Fig. 2). Vasoconstriction produces superficial necrosis of maternal tissue in the region of the implanted ovum similar to that noted in the pseudopregnant endometrium. This is proved by the observation of necrosis of maternal tissues some distance from fetal trophoblast.

Throughout most of the superficial portion of the pseudopregnant endometrium, vasoconstriction, formation and congestion of super-

and become capillary structures; whereas in the vera the spiral arteries extend to the surface. The younger specimen demonstrates this clearly. In our specimens there was only one instance found of invasion of an arterial wall.



Fig. 3.—The Edwards-Jones-Brewer ovum. The embedded blastocyst in this section is surrounded almost entirely by venous spaces which contain maternal blood. The villi are most numerous on the basal side of the blastocyst. The surface coagulum and depression at the point of entrance are shown in cross-section.

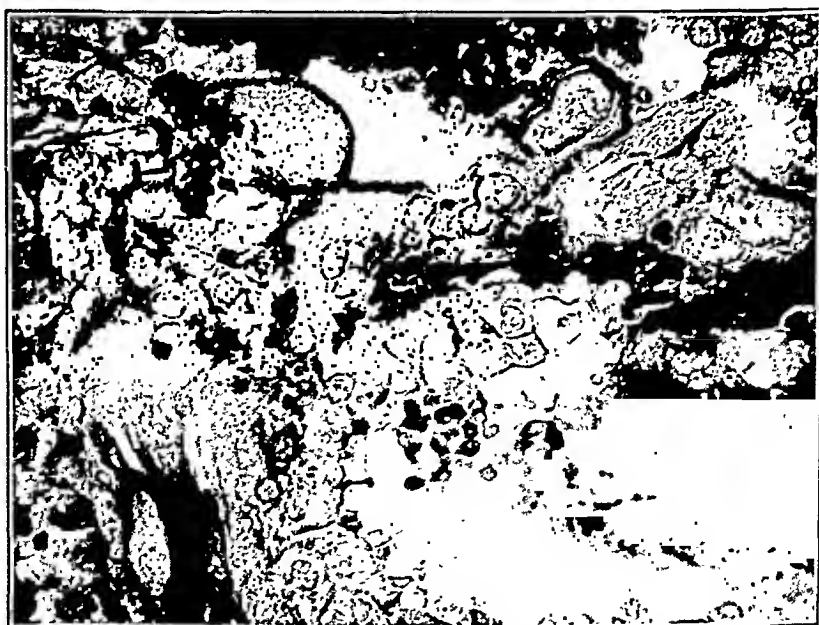


Fig. 4.—The Edwards-Jones-Brewer ovum. About this portion of the endometrial gland which contains blood there are masses of adjacent trophoblast. The gland epithelium is undergoing necrosis and in places is entirely wanting. This photomicrograph demonstrates the active destruction of gland tissue by the trophoblast.

Glands are invaded and their epithelium destroyed by adjacent trophoblast. In this manner blood enters the gland lumen (Fig. 4). That the necrosis of the gland epithelium is a result of the activity

ficial venous sinuses, superficial extravasation of blood, hemorrhage and superficial necrosis are consistently found, whereas, in early implantation (Edwards-Jones-Brewer ovum) these phenomena are limited to the region of the implantation site (Fig. 2). The local persistence of this phenomena is evidence that it plays a part in implantation. Wislocki and Hartman (1929) found the extravasation and bleeding to be limited to the implantation site.

Extravasation of blood, with some bleeding into the uterus, was demonstrated by Evans (1928) in the rat to be dependent solely upon maternal changes and not upon the presence of an embryo. This was possible, since in this animal deciduomas develop spontaneously. Krehbiel (1937) produced deciduomas and found similar extravasation and bleeding. Long and Evans (1920) applied the term "placental sign" to this type of bleeding which occurred frequently during the process of implantation. Corner (1921 and 1923) and Hartman (1932) suggested this vascular phenomenon was for the purpose of supplying blood for the implanted ovum.

Degeneration of maternal tissue in the penetration zone is in part a result of the vascular phenomena described above and in part is due to direct trophoblastic activity in early implantations. Proof of the former is found in the demonstration of the degeneration of tissue in regions remote from trophoblast. Since similar necrosis is demonstrated in endometrium during its cyclic changes, it is concluded that some of the necrosis observed in early pregnancy is a result of vascular phenomena and not dependent entirely upon the activity of the trophoblast.

TROPHOBLASTIC ACTIVITY

In the preceding chapter, it was shown that all the degeneration of maternal tissues in the penetration zone is not due to trophoblastic activity, as believed by most authors, but is due in part to the described vascular phenomena. This seems preferable to the theory of elaboration of ferments by the trophoblast in explaining degeneration of maternal tissue some distance away from fetal elements.

Evidence is present, however, which indicates that the trophoblast has a part in tissue necrosis in the penetration zone. A study of the blood vessels demonstrates fetal trophoblast invading capillary and vein walls (Fig. 3). This invasion is carried out by both individual wandering cells and masses of trophoblast. In many places the walls of the sinuses toward the fetal side are completely destroyed and replaced by trophoblast. The Edwards-Jones-Brewer and the Jones-Brewer I specimens supply multiple evidence of this. That arteries are rarely invaded is explained by the fact that as the arteries approach the penetration zone they rapidly lose their muscular coats

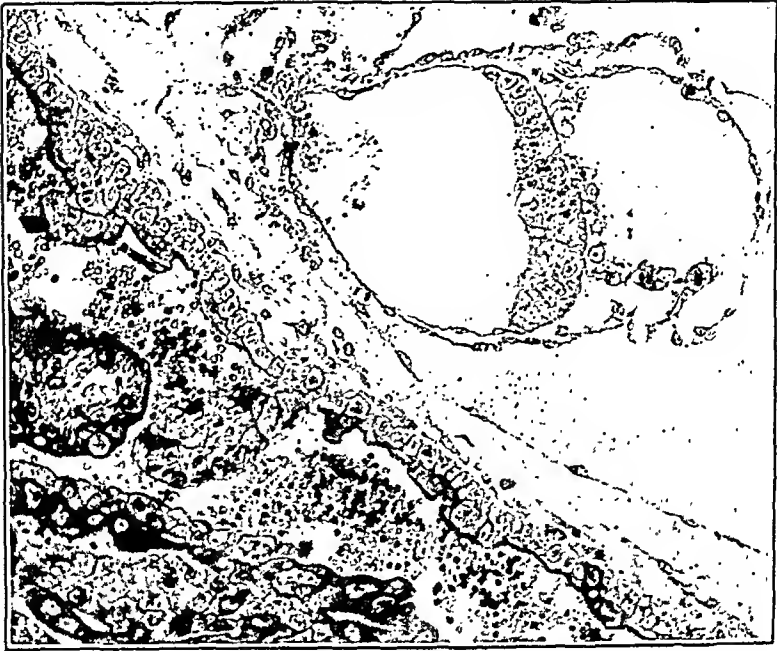


Fig. 5.—The Edwards-Jones-Brewer ovum. The embryonic disc is composed of a single row of columnar cells resting upon a definite basement membrane. The junction of the amnion with the disc is distinct. The amnion is larger than the yolk sac. The mesoblast of the chorionic wall invests the peak of the amnion.

The cells of the yolk sac are flat and elongated in all parts except beneath the disc where the primitive endoderm are cuboidal and are regularly arranged. There are no blood vessel or blood cell formations.

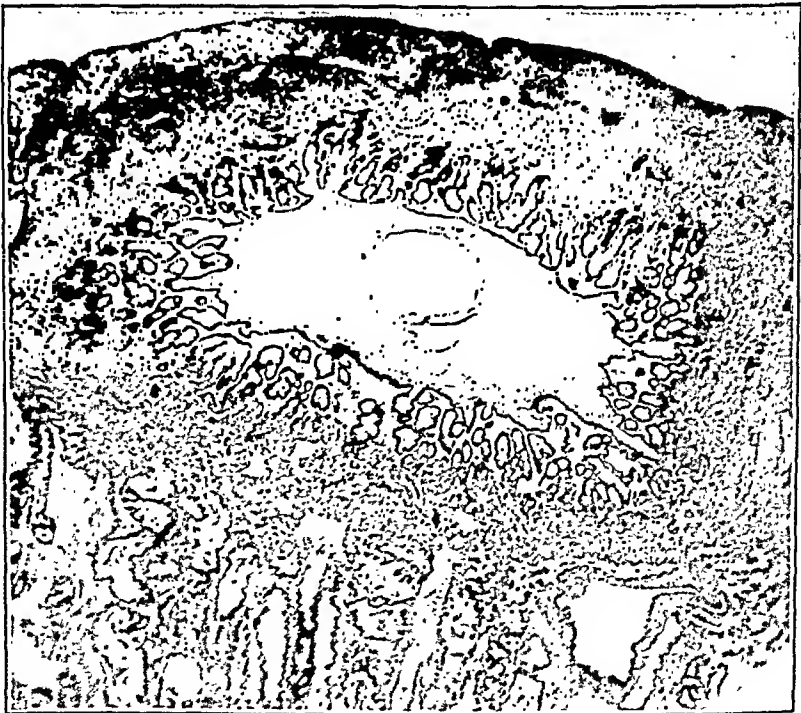


Fig. 6.—The Jones-Brewer ovum I. This photomicrograph of the implantation site shows the embryonic anlage attached at the most dependent pole. The villi are branched. About the blastocyst there are numerous dilated venous sinuses. The uterine glands are tortuous and filled with secretion. In this older specimen there is not as much hemorrhage about the implanted ovum as there is in the younger Edwards-Jones-Brewer and the Peters specimens.

of the adjacent trophoblast is indicated by the fact that only those epithelial cells near the trophoblast are undergoing degenerative changes (Fig. 4).

The reticulum throughout the penetration zone is arranged irregularly in strands and clumps. In places the clumps are thick, broken, and irregular strands surround masses of syncytial cells. These cells lying in the implantation cavity at the junction of maternal tissue have phagocytized strands of reticulum. Destruction of the reticular framework in many places is independent of adjacent trophoblast. It appears evident that the reticulum in many instances has been destroyed and broken up as a result of the superficial ischemia produced by the associated vasoconstriction (Brewer). When partly disintegrated, the strands are phagocytized by the syncytium.

Phagocytosis by the trophoblast is repeatedly noted. Red blood cells, leucocytes, lymphocytes, and reticulum are the most frequent maternal tissues phagocytized. The red blood cells rapidly lose their hemoglobin when ingested. Greenhill demonstrated iron in the fetal wandering cells and the above indicates the source of that iron.

The cytotrophoblastic cells also phagocytize maternal cells, chiefly red blood cells, lymphocytes, and leucocytes.

Glycogen was demonstrated in the fetal wandering cells in the Jones-Brewer I specimen. Presumably the glycogen was obtained from the uterine gland cells since this was the only other cell type in which glycogen could be demonstrated.

EDWARDS-JONES-BREWER OVUM

The Edwards-Jones-Brewer ovum was obtained by abdominal hysterectomy performed for multiple small fibroids and a dermoid cyst of the ovary. There was no abnormality of the menstrual cycle. The history is as follows: Last menstrual period Feb. 15 to Feb. 19, 1935. Period expected but failed to appear March 15, 1935. Operation (hysterectomy) March 20, 1935. The ovum was embedded on the posterior surface of the endometrium. Because of the small size no attempt was made to dissect it out grossly as was done in some of the other specimens.

The embryonic disc was cut in almost a transverse plane (Fig. 5). The body stalk and primitive streak region indicate the axis of the embryo.

The villi are short and not numerous (Figs. 3 and 5). They are more abundant on the basal side of the blastocyst. The syncytium covers the entire surface except the tips of the villi. In the outer portion of the implantation cavity the syncytium is identical to the primary syncytium described by Teacher, Bryce, and Grosser. It has a spun-out arrangement similar to their descriptions. Evidence of vacuolization of the syncytium as described by many workers is not noted to any great extent in this ovum. The formation of syncytium is described in conjunction with the Jones-Brewer I ovum.

Destruction of maternal tissue by the trophoblast is demonstrated. Venous sinuses, glands, and reticulum are the most frequently involved structures.

The embryonic anlage is attached at the most dependent pole of the blastocyst which is almost the universal rule (Fig. 3). The amnion is larger than the yolk sac in this specimen (Fig. 6). There are no blood vessel formations in the embryonic structure.

and staining qualities of the cytotrophoblast are demonstrated. The amount of granular cytoplasm increases until it is as dense as that of the syncytium. The staining qualities also increase in intensity.

In the Edwards-Jones-Brewer ovum similar changes are noted. Cytotrophoblastic cells are seen fusing together with a loss of cell membranes between them to form a multinucleated cell mass. These masses are in all respects like syncytium. Most of the secondary syncytium possesses a brush border, and numerous cytotrophoblastic cells also are shown to have faint brush borders. The cytotrophoblastic cells have a phagocytic activity similar to that of syncytium.

In addition to following the transitional phases in the formation of syncytium from the Langhans cells and cytotrophoblastic cells, and demonstrating the similar activities of these cell types, there is one phenomenon that strongly enhances this theory of syncytial formation. That is the fact that the Langhans cells disappear early in pregnancy. After disappearance of the Langhans cells syncytial formation

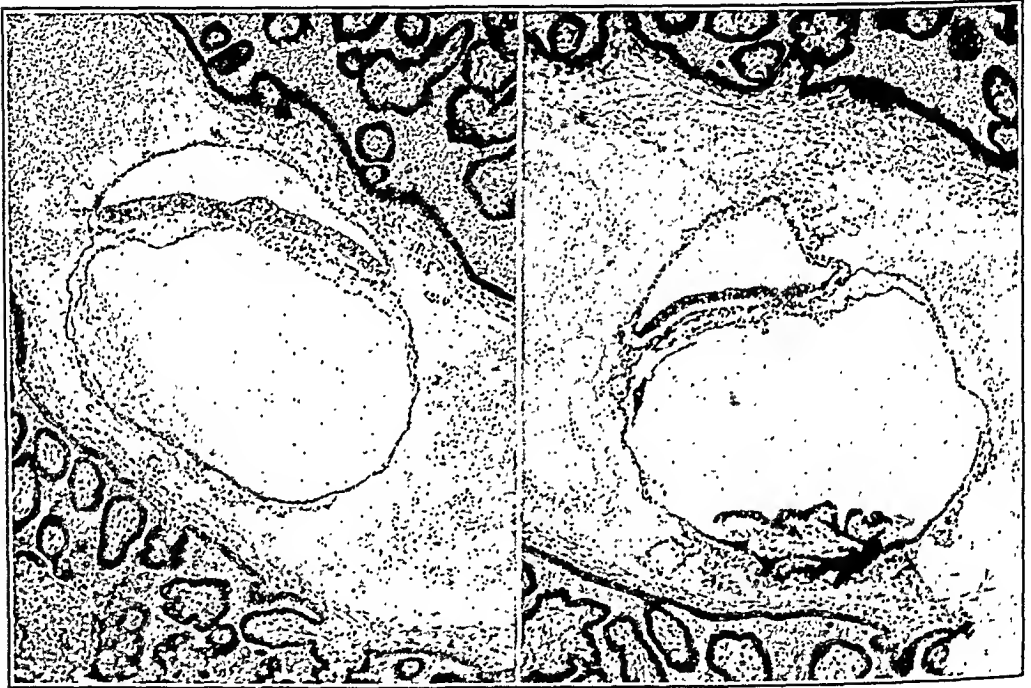


Fig. 7.

Fig. 8.

Fig. 7.—The Jones-Brewer ovum I. This is a photomicrograph of a slightly oblique section through the cephalic part of Hensen's node. The yolk sac is larger than the amnion. The embryonic disc is elevated in the region of Hensen's node. Laterally from the nodal tissue there is a growth of mesoblast between the embryonic plate and entoderm.

Fig. 8.—The Jones-Brewer ovum I. This section pictured is through the primitive streak. There is a distinct primitive groove with elevated parallel ridge. The lateral growth of mesoblast is at a maximum in this section. The streak cells are fused intimately with the ectodermal plate cells. There is no fusion with the entoderm at this point. The body stalk composed of chorionic mesoderm encloses the tip of the amnion.

is rare. This suggests that the Langhans cells have been used up in carrying out their function of forming syncytium.

The embryonic anlage is attached at the most dependent pole of the chorion (Fig. 6). There is a distinct penetration zone or zone of necrosis. Uterine glands, venous sinuses, and stromal tissues have been penetrated and destroyed. Blood vessels in various stages of development were present in the villi, chorionic wall, body stalk, and portions of the wall of the yolk sac. These vessels arise in situ.

The embryonic disc which has both a transverse and cephalo-caudal arching, is slightly broader than it is long. There is a definite Hensen's node (Fig. 7). The

The embryonic disc is flat and has no distinctive surface markings. The most striking feature is the absence of mesoblastic proliferation between the ectodermal plate and the entoderm (Fig. 5). The primitive streak is in the earliest developmental stage yet described for man. At the caudal end of the disc the basement membrane of the disc is disrupted and there is a piling up of the ectodermal and entodermal cells. Cells in mitosis are abundant, indicating a center of intensive growth. Streeter has shown in the pig that such a center is the site of the primitive streak.

The measurements made on the slides and the model are: External chorion 3.6 by 3.0 by 1.9 mm., internal chorion 1.85 by 1.71 by 1.01 mm., embryonic disc 0.209 by 0.177 mm., amnion 0.223 by 0.178 by 0.167 mm., yolk sac 0.197 by 0.160 by 0.120 mm., and greatest length of mesodermal villus 0.27 mm.

In this early specimen the disc is slightly longer than it is wide, while in the older Fitzgerald-Brewer I ovum the disc is circular in outline. This is true although the development and proliferation of a primitive streak in the latter specimen is well advanced. It has been suggested that the growth of tissue from the primitive streak causes elongation of the disc. The evidence obtained in the Edwards-Jones-Brewer, the Jones-Brewer I, and the Fitzgerald-Brewer I ova, however, indicates that the first proliferation of tissue from the streak is lateralward and results at times in a primary broadening of the disc. It is also apparent that there are other factors that account for the various shapes of the discs of very early ova. Streeter pictures variation in shape in young pig ova and the human ova are now shown to be similarly varied.

JONES-BREWER I EMBRYO

This ovum was obtained by vaginal hysterectomy. The operative procedure was a repair of an extensive laceration of the anterior and posterior vaginal walls and perineum. Vaginal hysterectomy was performed because of markedly relaxed uterine supports and a badly lacerated and eroded cervix.

After hospitalization and before operation the patient developed an upper respiratory infection and operation was delayed for fourteen days. During this time the patient, who had remained in the hospital, missed a menstrual period. This fact was not noted at that time. Her previous menstruation was normal. An exact coital history was obtained from both husband and wife.

Last menstrual period began Feb. 16, 1932, and ended Feb. 22, 1932. Coitus Feb. 26, Feb. 28, and March 4, 1932. Entered hospital March 10, 1932. Menstruation expected but failed to occur March 13, 1932. Hysterectomy (thirty-seventh day of cycle) March 24, 1932.

The body of the uterus after removal was 10.5 by 7.5 by 4.5 cm. and was without pathologic changes. The endometrium averaged 1 cm. in thickness. The ovum was embedded on the posterior endometrial surface, and it was depressed beneath the general level of the decidua (Fig. 6). The measurements are as follows: External chorion 8 by 7 by 4 mm., internal chorion 6 by 5 by 2.5 mm., embryonic disc 0.590 by 0.0782 mm., amnion 0.0592 by 0.0805 by 0.026 mm., yolk sac 0.072 by 0.079 by 0.076 mm., and primitive streak.

The blastocyst is covered with branched chorionic villi (Fig. 6). Syncytium composes the outer surface of the chorion and covers all of each villus except the tip. The Langhans cells project out beyond the ends of the villi as cell columns. It is a prevalent conception that these cells develop into syncytium. In the specimens of this report, more evidence is presented in accord with this view. In the Jones-Brewer I ovum the cells near the origin of the cell columns are dividing rapidly by mitotic division. The Langhans cells are also dividing rapidly. Syncytial formation is at a maximum during the stage of active division of these cells. Mitochondria are identical in these cells and in the syncytium. Changes in the amount

The embryonic disc was dissected out and photographs made (Figs. 9 and 10). From these the disc was oriented and cut in a transverse plane. The embryonic disc, which is circular in outline by geometric projection, has near its center an elevated Hensen's node. The cells of the node are arranged in a similar manner to that noted in the Jones-Brewer I specimen (Fig. 11). The radial arrangement, however, is more complete and extends over a greater distance. There is also more definite canalization.

The head process is in a very early developmental stage. The cells are grouped about a central point or in places about a central cavity or canal. The canalization is incomplete through the short extent of the cordlike head process. The cells of the head process are a direct continuation of the cells of the node. They are smaller than the node cells.

The caudal surface of the disc is interrupted in the midline by a deep primitive groove (Fig. 12). There is a primitive groove, streak, a cloacal membrane, and an allantois. The groove is somewhat tortuous and is deeper than that of the Jones-Brewer I ovum. Photographs of the normal ovum demonstrate the exact contour, size,

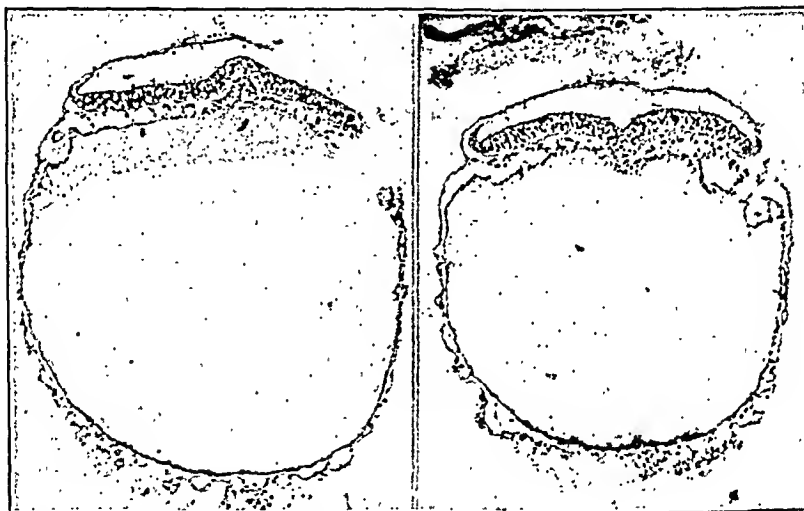


Fig. 11.

Fig. 12.

Fig. 11.—The Fitzgerald-Brewer ovum I. This is a photomicrograph of a section through the mid-portion of Hensen's node. Hensen's node is elevated and is composed of radially arranged cells. At the center point there is a small round cavity which extends cephalward through a few sections. Lateral extension of the mesoblast is slight.

Fig. 12.—The Fitzgerald-Brewer ovum I. This photomicrograph of a section through the caudal part of the disc shows a deep primitive groove with a large primitive streak area. There is extensive lateral growth of the mesoblast.

and axis of the disc. The latter is of value in orienting the specimen and in cutting the serial sections in an exact chosen plane. The slight tear of the yolk sac wall fortunately was of little consequence compared with the great value of obtaining actual photographs of the embryonic disc.

JONES-BREWER II OVUM

The ovum was obtained by hysterectomy done on the forty-ninth day of the menstrual cycle for uterine fibroids. There was no accurate coital history. The blastocyst was embedded on the posterior wall of the uterus, and projected 1 cm. above the general endometrial surface. Measurements made on the slides are: External chorion 12 by 6 mm., internal chorion 9 by 3 mm., embryonic disc 0.74 by 0.60 mm., and yolk sac 1.3 mm.

node is located near the center of the disc and is elevated above the surface. The cells comprising the node are arranged in a radial manner about several small slit-like cavities. This cell arrangement extends through to the dorsal surface of the disc but there is no opening demonstrable. This ovum presents the earliest stage in the formation of Hensen's node and neurenteric canal so far described in the human being. There is a primitive streak and groove (Fig. 8), cloacal membrane, and allantois.

FITZGERALD-BREWER I OVUM

This specimen was obtained by abdominal hysterectomy which was performed for the purpose of sterilization because of severe mitral heart disease. The patient had a normal thirty-day menstrual cycle.

Last menstrual period began June 25, 1934. Period expected but failed to appear July 25, 1934. Hysterectomy (thirty-eighth day of cycle) Aug. 2, 1934. An accurate coital history was not obtained.

The uterus was without pathologic changes. The blastocyst was embedded on the posterior wall of the endometrium and was elevated above the general level of



Fig. 9.

Fig. 10.

Fig. 9.—The Fitzgerald-Brewer ovum I. This photograph of the surface of the embryonic disc was taken after the embryonic anlage had been dissected out grossly. The irregular, dense tissue at the lower right is the body stalk. The disc is seen as an opaque structure with a clear-cut circular edge. At the center point there is a more dense region which represents Hensen's node. The yolk sac is the larger circular and less opaque structure.

This photograph was taken through the amnion.

Fig. 10.—The Fitzgerald-Brewer ovum I. This is a lateral view of the embryonic anlage showing the spherical yolk sac on top of which rests the opaque embryonic disc. The cephalocaudal arching of the disc is discernible. The elevation near the center of the disc is Hensen's node. The edge of the disc is quite even and regular.

The amnion is transparent except where the body stalk encloses it.

the decidua. The measurements of the ovum are: External chorion 10 by 9 by 5.5 mm., internal chorion 7 by 6 by 3 mm., embryonic disc 0.88 by 0.84 mm., amnion 0.89 by 0.86 mm., yolk sac 1.2 mm. in diameter, primitive streak including Hensen's node 0.42 mm., and prochordal plate and head process 0.1 mm.

The blastocyst was covered with branched villi. There was destruction of the uterine glands, stromal tissues, and venous sinuses as in the previous specimens. The anlage was similarly attached to the deepest pole of the chorion. There are blood vessel formations in the villi, chorion, body stalk, and yolk sac.

The anlage was dissected out grossly and the yolk sac was divided in order to obtain a photograph of the intact disc (Fig. 15). Under a dissecting scope the primitive groove and Hensen's node were readily visible. A head process is indicated by a dense opacity in front of the node.

FITZGERALD OVUM

The specimen was obtained by abdominal hysterectomy. The operation was performed because of multiple large fibromyomas. The patient had a normal thirty-day menstrual cycle, and there was no accurate coital history. The hysterectomy was performed on the thirty-fifth day of the cycle.

The uterus was as large as a large grapefruit. It contained many subserous and intramural fibroids. The endometrium was without gross pathologic changes. The blastocyst was embedded on the posterior wall of the endometrium in the fundal area and was definitely elevated above the decidual level. The measurements

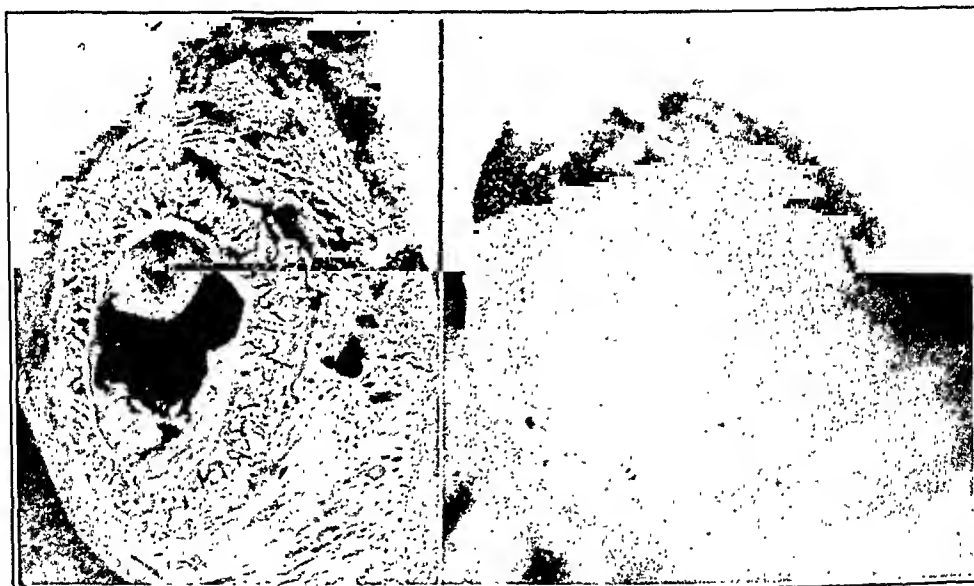


Fig. 14.

Fig. 15.

Fig. 14.—The Fitzgerald-Brewer ovum II. This photograph was made of the embedded blastocyst and embryonic anlage after the blastocyst had been cut away on either side of the anlage.

The villi are branched and completely surround the blastocyst. The magna is dense and is adherent to the yolk sac.

The yolk sac is larger than the amnion. The lateral edge of the disc is seen resting on the yolk sac.

Fig. 15.—The Fitzgerald-Brewer ovum II. Before making this photograph the embryonic anlage, as shown in Fig. 14, was dissected out and the basal half of the yolk sac was cut away. In this manner the more dense embryonic disc was made visible. The shape of the disc is oval with a narrowing in the caudal portion. The border is regular and distinct. Near the central point on the disc there is a still more dense region, the Hensen's node. Forward from this there is a pointed opacity which represents the head process. The primitive streak is suggested but not clearly defined.

of the ovum are: External chorion 14 by 12 by 9 mm., internal chorion 11 by 10.5 by 5 mm., embryonic disc 1.085 by 0.6 mm., amnion 1.1 by 0.7 mm., and yolk sac 1.3 by 1.2 by 1.4 mm.

There was a primitive streak including Hensen's node. The blastocyst was covered with branched villi which were as long as 1 mm. The ovum was sectioned in a plane which deviates but slightly from the longitudinal. All sections

The blastocyst was completely surrounded by secondary branched villi. The embryonic anlage was serially sectioned in a sagittal plane (Fig. 13). The cut sections were somewhat unequal in thickness. There is a primitive streak with lateral proliferation of the mesoblast, and there is a well-developed head process. The head process does not extend forward far beyond the node and the cells are between the embryonic plate cells and the entoderm. There is only occasional fusion of the head process with the entoderm. Hensen's node is a distinct elevation near the center of the disc. The cells of the head process and node are continuous. Because of the plane of section, a radial arrangement of the cells and a central cavity are not demonstrable. The disc is longer than it is wide. There is a definite allantois and cloacal membrane. The allantois, as in the other ova, is a tortuous structure lined with cuboidal epithelium. The body stalk, yolk sac, and chorionic villi contain definite vascular structures in which there are primitive blood cells. The body stalk is a more advanced structure than that of any of the other specimens described in this paper. Due to the trauma in opening the blastocyst in the fresh state, the body stalk and yolk sac were torn loose. These structures are considerably more advanced in development compared with those of the previously described ova.



Fig. 13.—The Jones-Brewer ovum II. This photomicrograph was made of a sagittal section near the midline of the embryonic disc. Hensen's node region is elevated. The nodal cells are densely grouped and cephalward there extends a loosely arranged column of cells, the head process.

The primitive streak is well developed and in places is fused with the entoderm. The arching of the disc is more abrupt than that of the other specimens of this report.

The body stalk is large and contains vessel formations. In it, also, there is a well-formed allantois. The allantois is seen to extend outward from the yolk sac.

The amnion is smaller than the yolk sac.

FITZGERALD-BREWER II OVUM

The Fitzgerald-Brewer II ovum was also obtained by hysterectomy. The procedure was done for the purpose of sterilization because of severe mitral heart disease. The pregnancy was normal in all respects. The uterus had no pathologic changes.

The patient had a regular thirty-day type of menstrual flow. The flow lasted from three to five days. The last menstrual period began forty-one days before operation.

The measurements made on the gross specimen with the aid of a dissecting microscope are: External chorion 10 by 6.4 mm., internal chorion 7.8 by 4.1 mm., and yolk sac 2.2.

Measured on the photographs and reduced to actual size, the disc is 1.48 by 1.205 mm. The blastocyst is covered with branched villi (Fig. 14). The villi are more numerous and longer on the basal side. The magma within is dense. The embryonic anlage is attached near one side of the chorion.

CONCLUSIONS

1. Six normal and complete presomite human ova are presented.
2. The vascular changes in the endometrium of early pregnancies are similar to those phenomena in the normal menstrual cycle.
3. These changes are vasodilatation and vasoconstriction, extravasation of blood, congestion of the superficial venous sinuses, and necrosis in the superficial portions of the endometrium.
4. These phenomena are primarily for the purpose of preparing a site for implantation of the human ovum.
5. The trophoblastic activity consists of invasion and destruction of maternal capillaries, venous sinuses, glands, reticulum, and stromal cells. Phagocytic activity is also demonstrated by the trophoblast.
6. Actual photographs of embryonic discs show them to vary in size, shape, and stage of development even though they are near the same age.
7. The "safe period" is not completely trustworthy since half of the human ova with critical data and complete descriptions were fertilized during the "safe period."

We wish to express our appreciation for the aid given by Dr. G. W. Barthelmez.

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were saved and arranged serially. A complete reconstruction of the embryo was made through the courtesy of Dr. George Streeter, and drawings of the model were made by James F. Didusch.

The embryonic anlage was attached to the deepest pole of the chorion. Blood vessel formation was evident in the villi, body stalk, yolk sac, and chorion. The embryonic disc was pear-shaped in outline. Hensen's node is a distinct and circumscribed elevation near the center of the disc. Extending caudally was a very deep primitive groove. A cordlike head process extended cephally from Hensen's node. There was a cloacal membrane and an allantois. The embryo was in its anatomic development slightly older than the Fitzgerald-Brewer II and the Jones-Brewer II ova. It was of considerable value in that it was perhaps the best preserved presomite embryo sectioned longitudinally, and as evidence of the fact that the shape of the disc may vary greatly in embryos of approximately the same development.

COMPARISON OF OVA

Arrangement of these ova according to age determinations is difficult, since the two most important factors in age determinations, the exact time of ovulation and the time required for fertilization, cannot be ascertained. Because of this, absolute age determinations cannot be made. In the past few years evidence as to the time of ovulation has been presented by various workers, both for the human being and the macaque. On the basis of such data there has been a general acceptance of a so-called "safe period." A study by Brewer of the young presomite human ova with critical data demonstrated that one-half of these young ova had their inception in the "safe period." This indicates that the time of ovulation in the human being is subject to wide variation and that a "safe period" is not entirely trustworthy.

A comparison based on the sizes, shapes, and stages of development is the method by which most ova are chronologically arranged. The size and shape of an embryonic disc are most accurately determined by actual photographs of the intact disc. The Fitzgerald-Brewer I specimen was dissected grossly and the disc photographed from various angles. By geometric projection of the photographs the disc is shown to be round. Although the disc is round there is an early head process formation. From the work which has previously appeared in the literature, one is led to suppose that there is an early elongation of the disc with the development of the primitive streak, Hensen's node, and the head process. In the Fitzgerald-Brewer II ovum actual photographs of the disc demonstrate an elongation of the disc but this elongation is relatively less than that of other reported ova.

Photographic lateral views portray accurately the arching of the embryonic disc and make it possible to obtain accurate measurements over that curve.

Such photographs reveal that variations in shape and size do occur normally.

Eleven of the cases recorded were private and nine were dispensary patients. The average age was about forty-two years, the youngest was thirty years and the oldest was fifty-one years. Most of the women were para ii or iii, were quite stout, had deep pelves, and a number of them had large pendulous abdomens. Several had had previous operations which complicated the procedures and interfered with the healing of the tissues. Most of these women had severe lacerations of the cervix, all of them had chronic infected cervixes, and in most cases the infection had traveled up through the tubes and along the uterosacral ligaments or along the bases of the broad ligaments, causing chronic pelvic disease (P.I.D.) with adhesions, thus making a clean, dry dissection impossible. Two patients who had marked cystoceles were nulliparas with large fibroids (Cases 0-1642 and 0-4327).

PROCEDURE

Preoperative Treatment.—The majority of patients upon whom a retrograde cystocle operation can be done are over forty years of age and in poor health due to chronic infections of the cervix, or a multiplicity of pathologic conditions in the abdomen, pelvis, and vaginal canal; many are tired or worn out from overwork or excessive loss of blood at the menstrual periods; some suffer from carious teeth and pyorrhea. The importance of getting them in the best possible condition by rest in bed and removal of any known foci of infection can readily be seen. Urinalysis, blood tests and counts, electrocardiographs, and basal metabolism tests should be done if indicated. All patients should be typed for transfusions which are often advisable on account of the extensive operations with their accompanying loss of blood and shock.

On the evening previous to the operation, the vulvae and abdomen are given the usual preparation. The patient is given an antiseptic douche, and a good night's rest is assured by the use of bromides, sedatives, or hypnotic drugs. Before being taken to the operating room she is given a hypodermic injection of $\frac{1}{4}$ gr. of morphine sulphate and $\frac{1}{150}$ gr. of atropine. Until the surgeon is familiar with the technic of this operation, it is advisable to insert ureteral catheters up to the kidney pelves to be removed at the end of the operation. This precedes the anesthetic, which is generally nitrous oxide plus oxygen and ether, administered by expert anesthetists. When inhalation anesthesia is contraindicated, and we think the operation can be completed within an hour and a half, spinal anesthesia is used. After the patient is anesthetized, she is placed in the lithotomy position, the vulvae and thighs are painted with a 2 per cent iodine solution which is washed off thoroughly with 70 per cent alcohol solution. The vagina is treated in the same way, care being taken to cleanse the vaginal fornices. After draping the patient, a Pezzar catheter is inserted into the bladder, the urine is drained off, the catheter is left in situ, and clamped off.

Operative Technic.—The cervix is then inspected, and if it is infected, it is either cauterized with the actual cautery or the cervical canal is dilated and an iodine tape is inserted into the uterine cavity, allowing the end to lie in contact with the cervix. If there is a relaxed perineum, with or without hemorrhoids, the technic described in my book, *Puerperal Gynecology* (Wm. Wood & Co., Baltimore, 1935), is followed.

The patient is then changed to the dorsal posture, and the entire abdomen starting from the pubic region to the breasts and laterally as low as possible is prepared

RETROGRADE CYSTOCELE OPERATION*

A PRELIMINARY REPORT

J. L. BUBIS, M.D., F.A.C.S., CLEVELAND, OHIO

(From the Service of Obstetrics and Gynecology, Mt. Sinai Hospital)

WHEN both an abdominal hysterectomy and a cystocele repair operation are indicated, the usual method is to repair the cystocele per vaginam and then perform a laparotomy for the hysterectomy. In the course of this procedure several of the newly placed important sutures must be cut in order to free the cervix from the vesicouterine ligament and the upper anterior portion of the vagina, thus increasing the danger of hemorrhage and necessitating a duplication of fascial and vaginal suturing. To eliminate these difficulties, I performed on April 4, 1935, a retrograde cystocele operation (Case No. 0-1642, described later). A total hysterectomy was performed first and then through the same abdominal incision a new support for the sagging base of the bladder was made by the repair and restoration of the torn and overstretched pubovesical or uteropubic fascia (George Gray Ward). This operation calls for very careful technic, as the bleeding from the plexus of veins near the urethra is often hard to control, and it is somewhat more difficult to build up a urethral support than by the classical method, but we find that this revision of order has several decided advantages. First, the retrograde cystocele operation eliminates the danger of cutting previously placed sutures. Second, after an abdominal hysterectomy has been performed, the herniation of the bladder is better exposed. Third, the exact position of the ureters can easily be demonstrated. Fourth, after the repair of the fascia by this method, the implantation of the round ligaments on the anterior cuff of the vaginal wall helps give additional support to the bladder. Fifth, there is a slight saving of time.

This report covers a series of twenty retrograde cystocele operations, although five more have since been performed in addition to this number with excellent results. In all these cases, abdominal hysterectomies were definitely indicated. We prefer to do complete hysterectomies unless the cervix is absolutely normal or the patient's condition does not warrant this radical procedure. A retrograde cystocele is best performed when the uterus and cervix have been removed. We did several retrograde cystocele operations after supra-cervical hysterectomies, but on account of incomplete drainage, this was discontinued.

*Read at the Eighth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Detroit, Mich., October 15 to 17, 1936.

A transverse incision through the peritoneum posteriorly just above the utero-sacral ligaments is then made and the flap is pushed downward. The uterus is now pulled up as high as possible and the cervix is palpated through the vaginal walls. An incision is then made through the anterior vaginal fornix, the cervix is grasped with a bullet forceps and pulled upward. The incision is then carried completely around the cervix until the uterus can be removed. All bleeders are clamped, care being taken to include the vaginal mucosa and the adjacent peritoneum, especially laterally and posteriorly. The upper part of the vaginal canal is then wiped dry from above and repainted with a 2 per cent iodine solution. A running interlocking No. 1 chromic catgut suture replaces the clamps (inset on Fig. 2). A clean abdominal pack is then inserted, and the anterior tape which held the bladder out of the way is removed. The anterior peritoneal flap is grasped by several Ochsner clamps, as is the margin of the anterior vaginal cuff (Fig. 3).

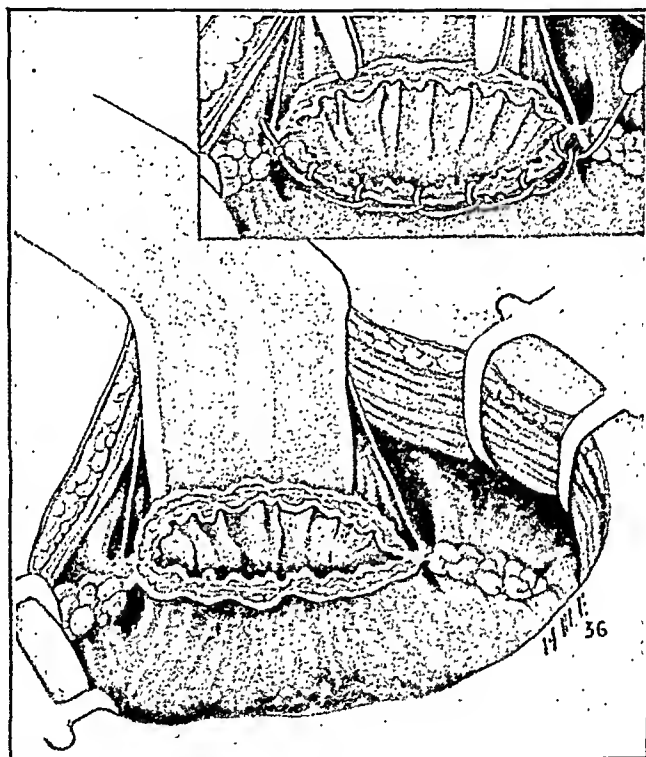


Fig. 2.—Broad and round ligaments cut and tied. The bladder is held back by a narrow retractor. Inset shows the bladder held back by a narrow retractor, two clamps on the edge of the pubovesical fascia, the anterior vaginal wall and a continuous interlocking suture connecting the margins of the posterior vaginal cuff with the peritoneum.

The bladder is then carefully separated from the remains of the pubovesical fascia down toward the urethra until the Pezzar catheter can be palpated. The bladder is held out of the way by a firm, narrow ribbon or Deaver retractor and the fascia is stripped away from the anterior vaginal wall. The fascia may be a thick overstretched sheet of tissue, it may have a hernial pouch in the center with firm edges (so-called Pillars of the Bladder), or it may be very thin, ragged and torn down through the center to the urethra (Fig. 4).

The difficulty encountered in separating the bladder from the fascia and the latter from the vaginal wall depends on the thickness and strength of the remains of the fascia, on the success of getting the lines of cleavage, and on the amount of scar tissue present. The ureters are practically always out of the way if the

by the iodine-alcohol or other antiseptic method. The drapes are then arranged exposing only the field of incision. Unless there is a midline incision from a previous operation, we prefer the Pfannenstiel or low transverse incision made at the margin of the pubic hair, through the skin, subcutaneous fat and fasciae. All bleeding points are controlled by plain No. 0 catgut ties. Ochsner clamps are then placed at the edges of the cut fasciae and the lower flap is dissected down to the pubic bone. The upper flap is freed in the midline from the muscles and fascia as high as possible, being careful to avoid the two small ilio-hypogastric nerves and their accompanying blood vessels. The two recti muscles are separated and the peritoneum is incised longitudinally. On account of the low position of the incision great care must be exercised to avoid an incision into the bladder. The patient is then placed in the high Trendelenburg position. A Balfour abdominal retractor is in-

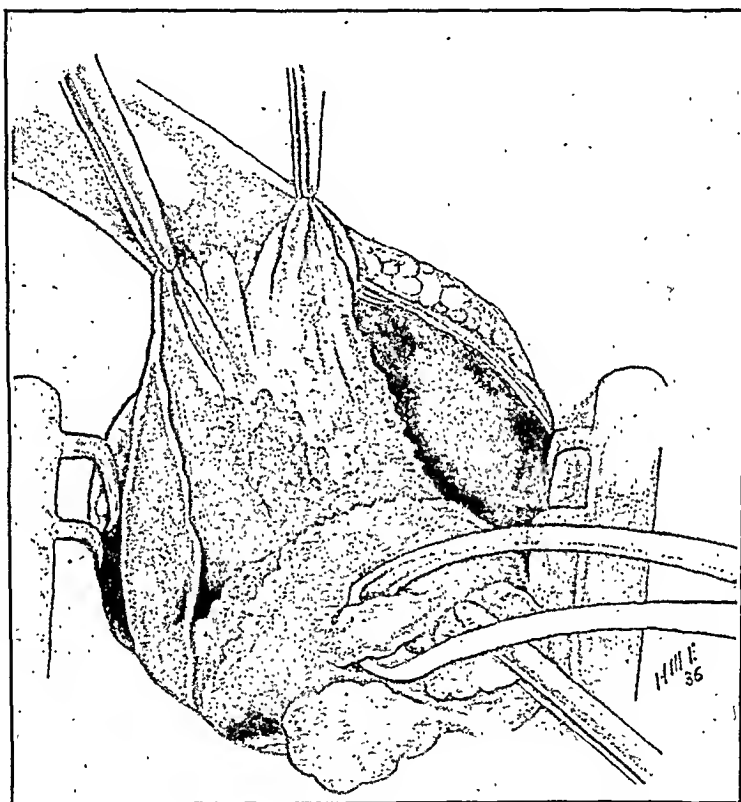


Fig. 1.—Bladder separated from the anterior wall of the uterus.

sented, the pelvis is examined, and a decision is made whether a total hysterectomy alone or with removal of one or more adnexa is to be done. One large gauze pack is so placed that it will be sufficient to keep the abdominal contents out of the pelvis. This is also helped by a wide, flexible ribbon retractor. A large angle retractor placed at the pubic end of the incision helps to give a good exposure. The round ligaments are clamped about an inch from the uterine cornuae, cut and tied. The peritoneum about an inch above the bladder is then incised between the stumps of the round ligaments and dissected down by blunt dissection as far as possible (Fig. 1). The vesicouterine ligament must be incised and the base of the bladder is lifted up and forward by a firm, narrow, ribbon retractor protected by a narrow tape. The broad ligaments are clamped, cut, and tied on both sides down to the isthmus of the uterus. The uterine arteries and their large branches are then cut and tied close to the cervix.

sutures on small Bubis needles, starting as low toward the urethra as possible and working upward toward the abdominal incision, incorporating a small amount of bladder, vagina, or both tissues in the sutures (Fig. 6). This helps to control oozing and bleeding points and obliterates any "dead" spaces. After the new support for

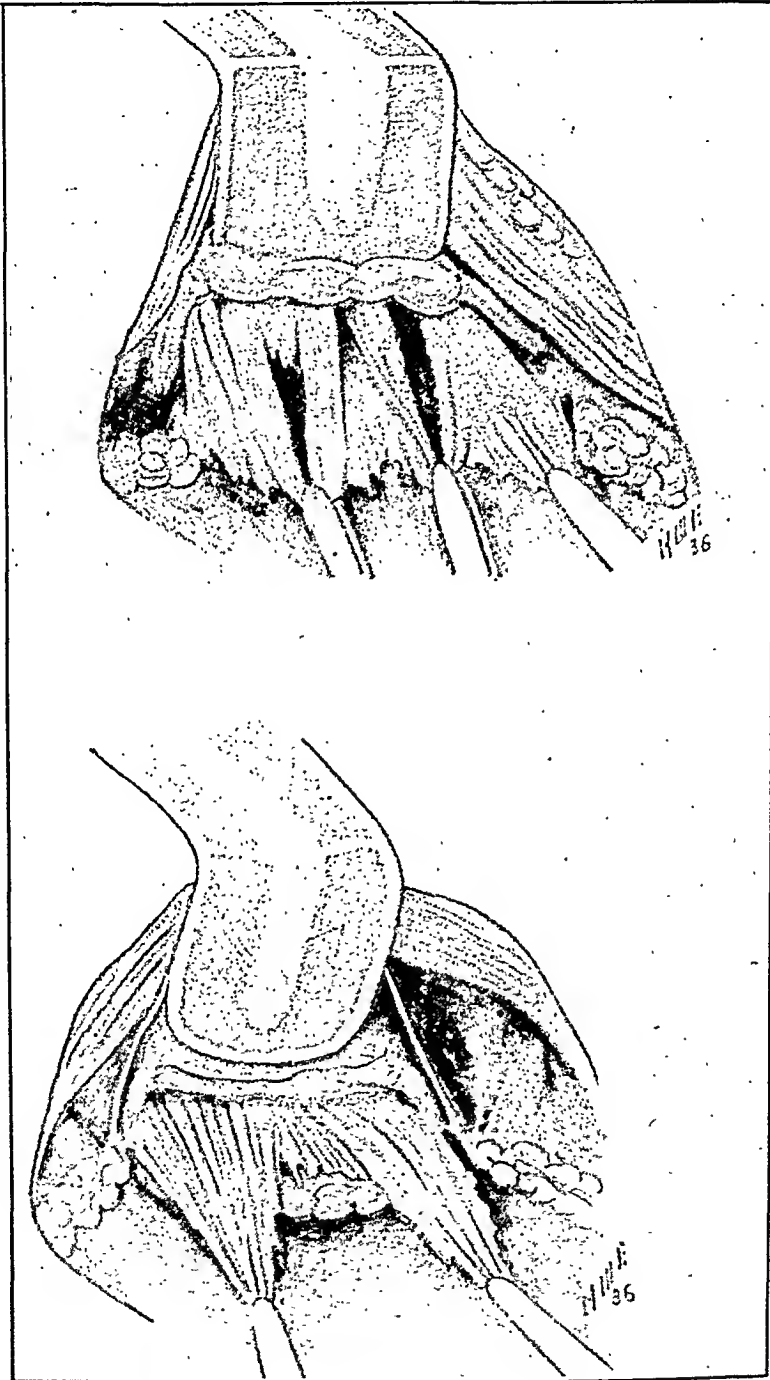


Fig. 4.—Two of the types of fascial remains encountered in our series.

the bladder has been finished, the slack of the anterior vaginal wall is taken up by tension on the Ochsner clamps attached to its edge and two or more plain catgut sutures obliterate the space between the vagina and the bladder, or a wedge-shaped excision may be made with the base toward the abdominal incision. The two edges

right technic is used, although we have occasionally exposed them for anatomic study without any serious after effects. (Cases 0-5014, 0-5446, 0-4327, 0-3809, 0-3872.) The ureters may be kinked or caught in the sutures when the uterus is pulled high in the pelvis (Fig. 5, *B*), when the uterine arteries are clamped and

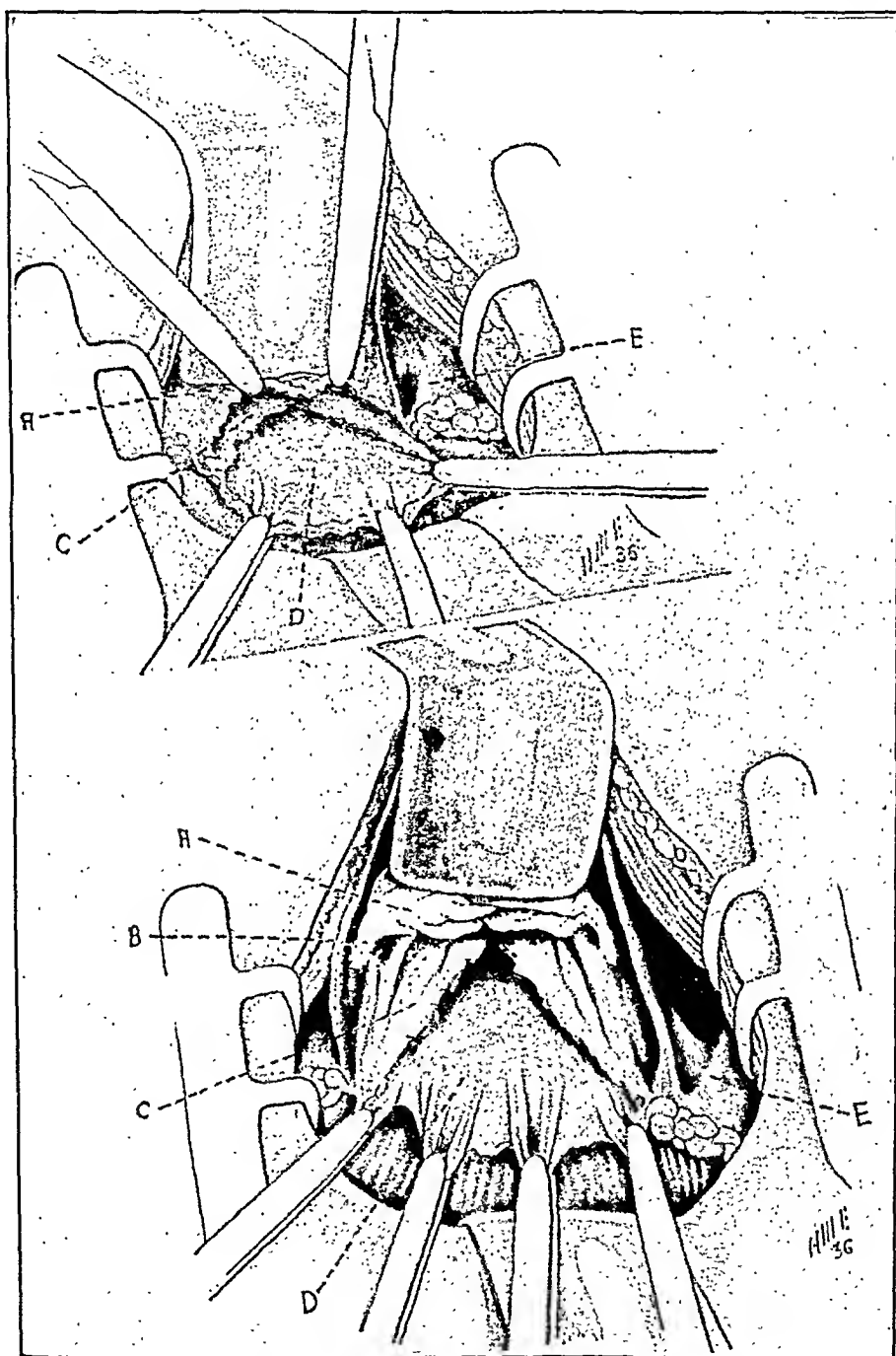


Fig. 3.—*A* is the base of the bladder. *B* is the left ureter. *C* shows the remains of the pubovesical fascia. *D* is the anterior vaginal wall. *E* is the right round ligament.

tied, or they may become closed by edema and swelling of the surrounding tissues, thus causing signs and symptoms of acute urinary retention (No. P-2078).

The next step is the most difficult part of the procedure. This is the reconstruction of the pubovesical fascia, with either interrupted or continuous No. 2 catgut

are then brought together in the midline by an interlocking continuous or interrupted No. 1 chromic catgut suture. The upper part of the vaginal canal is left open, although the angles are coapted by sutures (Fig. 5, inset). A large Penrose or cigaret drain may be inserted into the vagina and the abdominal end is placed in the perivesical spaces or carried down into the culdesac. This is removed within a week per vaginam. We have not formed any definite conclusions as to whether patients have a better recovery with or without drains.

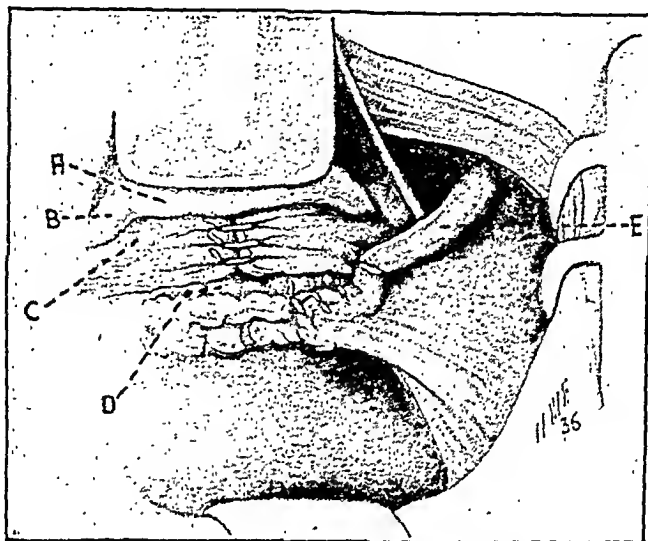


Fig. 7.—A is the bladder. B is the left ureter. C is the reconstructed pubovesical fascia. D is the anterior vaginal cuff. E shows the right round ligament attached to the fascia and the anterior vaginal cuff. We now attach the round ligament to the vaginal wall only.

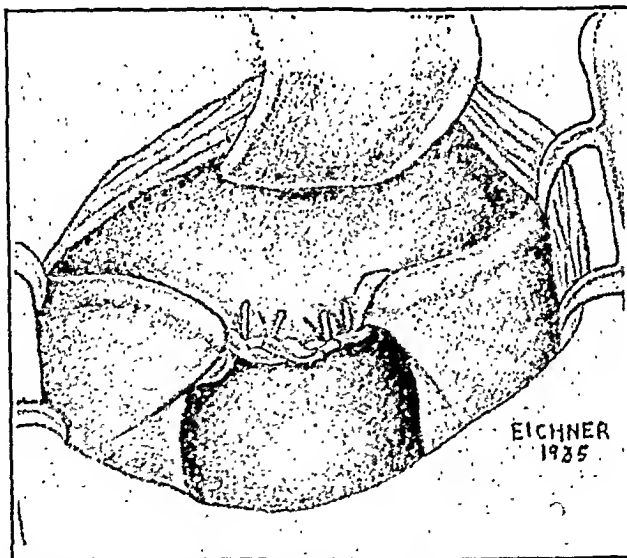


Fig. 8.—Shows the anterior peritoneal flap with the attached bladder sewed to the uterosacral ligaments, covering the vaginal orifice and all raw surfaces.

An important step in the success of the operation is the suturing of the round ligaments to the anterior cuff of the vagina not to the fascial plane as in Fig. 7. This helps to keep the anterior vaginal wall taut, gives added support to the bladder, and prevents future procidentia of the vaginal wall. The anterior peritoneal flap with the attached bladder is then sewed over the vaginal orifice to the uterosacral

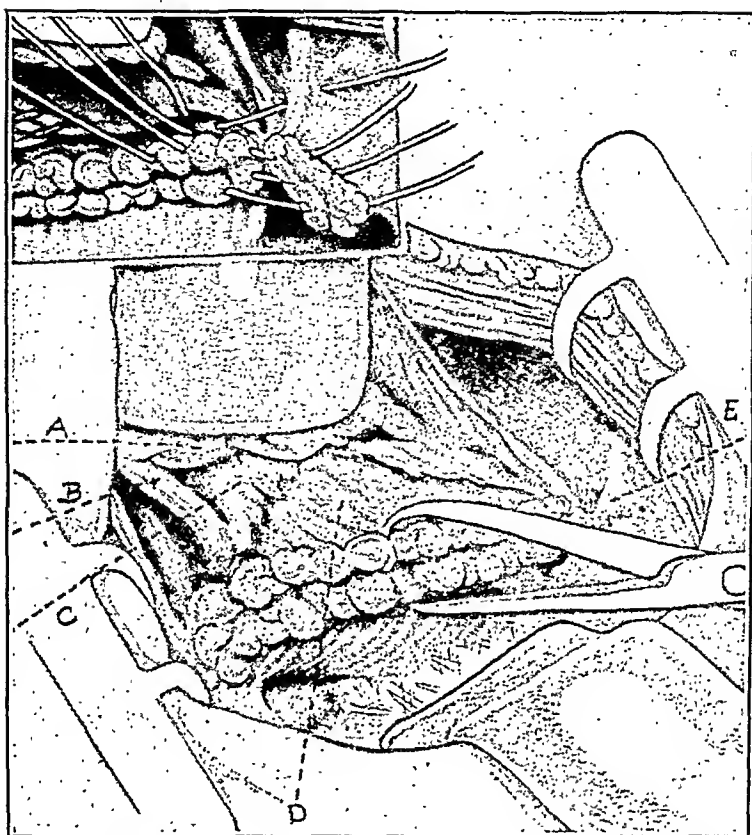


Fig. 5.—Same as Fig. 3. *Inset.* Shows coaptation of the right broad ligament stump and a suture on the round ligament which is pulled over the upper portion of the anterior vaginal thus preventing procidentia of the vagina.

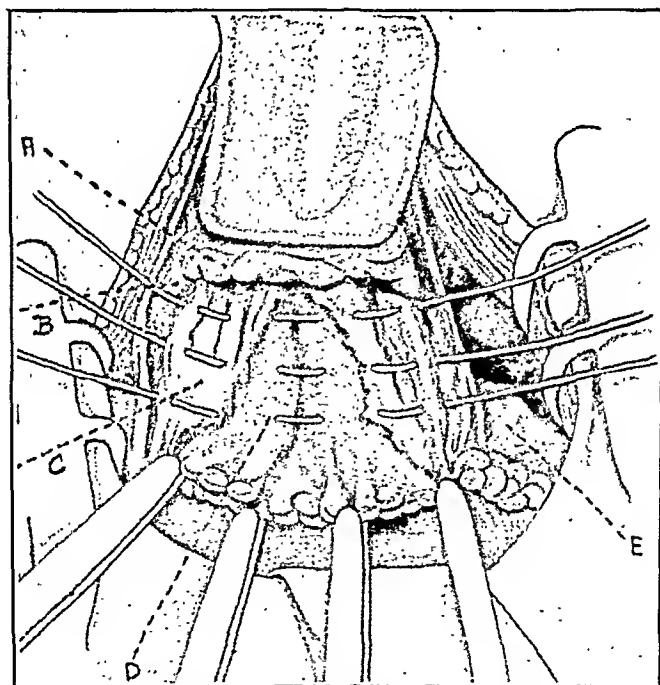


Fig. 6.—Sutures placed through the so-called pillars of the bladder, grasping the anterior vaginal wall.

and a fixed fibroid uterus extending to within 3 fingerbreadths of the umbilicus. The operation consisted of a vaginal preparation, a panhysterectomy (both tubes showed marked hydrosalpinx and were matted together with the ovaries), and a retrograde cystocele operation. A cigaret drain was placed in the culdesac and the other end was inserted in the vagina. The appendix was then taken out. Total anesthesia was eighty-five minutes. She developed a wound infection which had to be probed, and Dakin's tubes were inserted. She left the hospital twenty-one days after the operation, the wound well healed, and the urethra well up under the pubic arch.

POSTOPERATIVE TREATMENT

When the patient is returned to her bed, the foot of which is elevated, she is given an intravenous and subcutaneous infusion of glucose and saline solution, her blood pressure and pulse are taken every half hour, and she is watched for vaginal bleeding. Pain and restlessness are controlled by morphine or other sedatives and hypnotics; carbon dioxide and oxygen inhalations, change of posture or position, or intravenous injections of 20 per cent glucose solution are given for respiratory complications. Gastric lavage or gastric decompression by the Levine tube for a dilated stomach, pitressin or other intestinal stimulants, medicated enemas and hot stupes are helpful in the control of intestinal distention. The bladder is drained continually during the first twenty-four hours, and then the Pezzar catheter is clamped and the urine is drained off every two to six hours, followed by an instillation of 2 ounces of 1:4000 neutral acriflavine solution or 1 ounce of 10 per cent argyrol solution. The patient is given some urinary antiseptic by mouth until the catheter is removed or until the urine becomes normal. Tonics, fresh air, mild cathartics, increase in diet, etc., are given as indicated. The general condition of the patient determines the length of the stay in the hospital. The longest number of days was thirty-four, and the shortest number of days was twelve, with an average stay in the hospital of 18.55 days for this series.

COMPLICATIONS

If careful attention is given to the operative technic in gently separating the tissues and controlling hemorrhage, the number and type of complications should not be any greater than those following a total hysterectomy alone. There is a possibility of damage to the bladder unless extreme care is exercised. The following illustrates a case in which difficulty was encountered due to an accumulation of perivesical exudate and edema, and kinking of the ureter. Mrs. R. D., No. P-2078, dispensary patient, aged thirty years, para ii, admitted to the hospital May 5, 1936, complained of pain in the lower abdomen, low backache, leucorrhea, frequent burning micturition, and a protrusion from the vagina. Following the birth of her first child, seven years before, she had had a repair of the cystocele, a partial amputation of the cervix, left salpingo-oophorectomy, and appendectomy. Three years later, her second child was born.

Examination on entrance to the hospital showed a marked cystocele, a lacerated infected cervix extending to the fornices. The uterus was in a retroverted position and adherent. On May 6, 1936, separation of adhesions, a total hysterectomy and retrograde cystocele operation were performed. Much difficulty was encountered due to old scar formation from the previous operation and the inflammation of the bases of the broad ligaments. The length of anesthesia was one hour and forty minutes, and the time of operation was one hour and twenty minutes. She was returned to her room in good condition. On May 10 she complained of pain in the right kidney region and the temperature rose to 102° F. Her condition remained

ligaments (Fig. 8). At each angle a circular invaginating suture is placed which grasps the vesical peritoneum, the round ligaments, the stump of the infundibulopelvic ligament, the posterior broad ligament, the uterosacral ligament and is brought out through the vesical peritoneum. The parietal peritoneum and the rest of the abdominal incision is closed in layers. The ureteral catheters are then removed but the Pezzar catheter is left in situ for two to six days. Before the patient leaves the operating room she is given 90 per cent oxygen with 10 per cent carbon dioxide inhalations for about two minutes. This stimulates deep breathing and has materially decreased postoperative lung complications.

Inasmuch as all of these women were subjected to prolonged anesthesia and to a multiplicity of operative maneuvers due to marked pathologic changes in the genital tract and reproductive organs, it is very important to work rapidly with as little trauma and loss of blood as possible. The longest time of anesthesia was two hours and forty minutes while the shortest time was one hour and twenty-five minutes, with an average time for the series of two hours and five minutes. The longest time of the abdominal operation was two hours, the shortest one hour, and the average time of abdominal operations in the series was one hour and twenty-nine minutes. Following the operation, if the patient shows signs of shock, she is transfused with 500 to 700 c.c. of whole blood immediately.

In order to demonstrate extreme cases, a brief résumé of two operations follows, one of which entailed the longest and the other the shortest anesthesia.

CASE REPORTS

Mrs. R. G., aged forty-five years, para v, was admitted to the hospital July 30, 1935, complaining of pain in the lower abdomen, burning frequent micturition, and irregular and profuse menstruation. Examination showed a very marked cystocele, rectocele, and a moderate urethral prolapse, a large hypertrophied and infected cervix, and a large boggy uterus. On account of her obesity she was kept in bed and given 5 gr. of desiccated thyroid extract twice daily until her operation on August 3. The procedure followed was: vaginal preparation, insertion of a Pezzar catheter, repair of a rectocele, a change from the lithotomy position, an abdominal preparation, a lipectomy, panhysterectomy, retrograde cystocele repair, appendectomy, and abdominal closure. There was considerable bleeding from the bladder base. The total anesthesia was two hours and forty minutes, with abdominal operation time of two hours. The pulse at the beginning of the operation was 100 beats per minute, which decreased to 85 beats per minute at the end of the operation. At 1:30 P.M., two hours after the operation, her blood pressure was 82/56. She was then given 750 c.c. of 2½ per cent glucose solution intravenously. At 2:30 P.M. the blood pressure was 92/87. She was transfused with 750 c.c. of whole blood by the Kempton Brown method at 8:00 P.M. The following day her blood pressure was 108/78 and gradually rose to normal. On August 5 she had a cough and coarse râles in her chest. She was given 50 c.c. of 20 per cent glucose intravenously. Her temperature rose to 102° F. on this date, and gradually decreased to 99.6° F. on August 10. The Pezzar catheter had been removed on August 8. She complained of urinary frequency for several days, and many bacteria were found in the urine. She left the hospital August 18, fifteen days after the operation, with perfect operative results.

The shortest anesthesia was given in the case of Mrs. G. B. (Case O-1462), aged forty-three years, who was admitted to the hospital April 4, 1935, complaining of leucorrhea, urinary frequency, nocturia, backache, and increased menstruation. She had had three miscarriages, up to six months. She also gave a history very suggestive of an old gonorrheal infection. Examination showed a moderate cystocele

DISCUSSION

DR. CARL P. HUBER, CHICAGO, ILL.—In the literature dealing with the repair of cystocele there are numerous procedures described which have as their distinguishing characteristic an abdominal approach to the bladder area.

The first of these operations was described by Byford in 1890. He operated through the inguinal canals and fastened the tissue on either side of the bladder in the inguinal wounds. Lowson in 1898 reported a procedure in which the bladder is mobilized and pulled upward where it is sutured in approximation to the anterior abdominal wall by a flap of peritoneum containing the urachus and the obliterated hypogastric arteries. Dickinson in 1903 suspended the bladder, usually with the uterus, by actually fixing it to the rectus muscle and fascia.

William Polk in 1909 first described an operation in which the bladder was separated from the uterus and the dissection carried down the anterior vaginal wall to the urethra. The anterior vaginal wall and the fascia under the bladder were then plicated. The operation also included shortening of the round ligaments, while the sacro-uterine ligaments were pulled forward to the anterior portion of the cervical stump. He emphasizes the dangers inherent in the procedure of traumatizing the bladder wall and ureters. In 1921, Lillian Farrar described a similar procedure which she combined with abdominal hysterectomy. The abdominal operation was preceded by any necessary repair of the posterior vaginal wall and cervix. Following these, a supravaginal hysterectomy is performed, the bladder separated from the anterior wall and fastened on a shelf produced by the sutured cervical stump, broad ligaments, round ligaments, and sacrouterine ligaments.

The speaker today offers an admirable description of an operative procedure which technically appears more difficult than a combined vaginal plastic and abdominal hysterectomy. In the absence of personal experience with the particular procedure there are some questions which come to mind before we can wholeheartedly endorse the operation.

1. Is there really an advantage to the procedure over that of the usual combined vaginal and abdominal approach? Technically it seems to me that the advantage is with the combined approach, for certainly the visualization of the operative field is better, and if care is used in placing the sutures from below, I do not believe that there is serious danger of subsequently cutting them.

2. Do improved results warrant a procedure which is more difficult? The author reports 14 cases with perfect results and six cases which showed marked improvement. This surely is commendable, but I do not believe it is superior to the results of vaginal repair. In a series of 100 cystocele repairs reported from the University of Michigan by Norman F. Miller in 1928, there were 94 patients who were cured or definitely improved, 72 of these were reported as completely cured. Incidentally, in this group coincident hysterectomy was indicated in only eight cases. Six were cured and two definitely improved following the operation.

In conclusion, I wish to state that I do not pretend to condemn a procedure without giving it a fair trial. On the other hand, I do not wish to recommend it without due consideration of its merits. I believe that Dr. Bubis should be congratulated upon his attempt to stimulate this plan of attack, but suggest, however, that because of its character this procedure will be limited in its application and should only be attempted by one skilled in pelvic surgery.

DR. BUBIS (closing).—This operation is not intended for all cystoceles. After doing a cystocele repair from below and then going in above to take out the uterus, I have inadvertently cut some of the sutures which I had originally placed. It may be very difficult under these circumstances to control the bleeding and the re-suturing of the upper part of the vagina.

about the same for several days, and on May 14, one week following operation, Dr. Wm. Rosenberg cystoscoped her and made the following notation: "Bladder urine slightly cloudy and purulent. The bladder capacity is slightly decreased and the patient does not tolerate distention on account of bladder spasm. There is a general cystitis present with numerous flakes or pus and bloody mucus. There is no evidence of diverticulum, but there is a marked deformity of the base of the bladder and the anterior vesicle wall due to the operation. The ureteral orifices are somewhat more lateral than normal, and there is a moderate amount of injection around the left ureteral orifice. The right ureteral orifice is edematous and an impassable obstruction was met 2 cm. above." A retrograde pyelography was done the next day which showed the dye in the left kidney, ureter and bladder, and an obstruction was noted in the right ureter near the bladder. On May 16 there was a profuse sanguineous purulent vaginal discharge. The urine showed 2-plus albumin. On May 20, the urine was much clearer with a moderate number of pus shreds present. Cystoscopic examination showed a mild general cystitis. The deformity noted above had disappeared and the bladder was practically normal in outline. Catheters were passed up both ureters without difficulty. A right pyelogram showed normal filling of kidney, pelvis, and calyces. Slight dilatation of the entire right ureter was present. The upper part of the ureter showed a slight angulation and kinking with apparently no interference with drainage. Two months later she was in good condition, her urinary symptoms had cleared up but examination showed that the anterior wall was slightly sagging.

END-RESULTS

A series of perfect results from any type of cystocele operation is never obtained. There are so many factors involved in the correction and healing of diseased or overstretched tissues in a potentially infected field that any improvement in the comfort of the patient and restitution of the structures to a condition as nearly normal as possible is all that we can hope to obtain.

In this series of twenty cases 14 showed perfect results and 6 showed very marked improvement over their previous condition, three months to a year after the operation.

CONCLUSIONS

1. This operation was devised for those patients who have cystoceles and pelvic pathologic conditions in which total abdominal hysterectomies are indicated.
2. Careful technic, proper lighting facilities, and good assistants are very important.
3. Ureteral catheters are good guides until one is familiar with the landmarks and the technic of the operation.
4. A retention Pezzar catheter also helps to outline the urethra and the adjacent portion of the bladder.
5. Implantation of the round ligaments into the cuff of the anterior vaginal wall beneath the bladder helps to lift the anterior vaginal wall and give added support to the bladder.
6. Restitution of the pubovesical fascia by the abdominal approach eliminates the danger of cutting previously placed sutures and has been proved feasible in the retrograde cystocele operation.

two pituitary gonadotropic hormones (follicle-ripening and luteinizing); (5) the significance of the anterior pituitary-like principles (prolan) found in the urine of pregnant women; (6) the chief indications and the limitations of organotherapy. To say that we know all about these subjects would be absurd, for most of them are still the subjects of active study and lively discussion. And yet it may fairly be said that we have a good working concept of reproductive endocrinology, lending itself readily to the additions and corrections which each year will bring.

My purpose today is to discuss, along rather broad lines, some aberrations of this normal function, more particularly a few which have not received as much attention in the literature as their interest or importance would seem to justify. Things may go wrong with the ovary from the earliest stages of its development. The zygote is always bisexual, and whether a gonad is to develop into an ovary, a testis, or an ovariostestis is dependent upon the genic balance of the zygote. At its very origin, therefore, gonadal development receives an initial impulse and direction from certain uncontrollable chromosomal factors, and it is this primitive impulse, colored in various ways by the later unfolding of endocrine forces, which must be invoked in the explanation of so many cases of intersexuality. In the differentiating processes of early life, there is every reason to believe that the motivating force is not of endocrine nature, and that segmentation and differentiation proceed according to a foreordained pattern because of some germ-cell force which, for the present, is as mysterious as the life principle, and which might indeed almost be considered the life principle itself. Any one who has seen moving-picture films of the dividing rabbit egg must have been impressed with the remarkable precision with which each new cell falls into its appointed place, just as football players do when the signal is flashed.

Attractive as it would be to explain the early development of the uterus on the basis of endocrines, there is no evidence to substantiate this view, and it seems likely that early genital development and differentiation are not different from that of other organs and tissues. Even in its undeveloped form, however, the uterus, as well as the mammary gland, already possesses a remarkable sensitivity to endocrine influence, as indicated by the fact that maternal hormones bring about an increase in the size of the uterus so that it is larger at birth than it is shortly afterward, that the withdrawal of these hormones may actually bring about a single pseudomenstrual bleeding a week or so after birth (non-menstrual genital hemorrhage of the newborn), and that mammary growth and even lactation may appear in either the male or female child.

We know very little, too, about the possible endocrine importance of the ovary in the prepubertal years, though we do know that follicles mature to certain stages of development and that at least some estrin is produced a long while, even several years, before the actual occurrence

This operation is an anatomic reconstruction of the main support of the bladder, that is, the reconstruction of the pubovesical fascia with the additional support to the bladder by the implantation of the round ligaments into the anterior vaginal cuff under the bladder, which also helps to stretch the vaginal tube.

We are very careful when we say we have a cured case. If there is any deviation from the normal anatomic structure, we call it a failure. Without a strict use of this word we might include several cases in which the patients are in good condition without any sagging.

SOME LESS GENERALLY RECOGNIZED ASPECTS OF GYNECOLOGIC ENDOCRINOLOGY*

EMIL NOVAK, M.D., BALTIMORE, MD.

(From the Gynecological Department, Johns Hopkins Medical School)

THE prime function of the ovary is the production of ova. In spite of the all-importance of this function from a racial standpoint, the ovary is not at all essential to the life of the individual woman. On the other hand, the removal of other endocrine glands whose function seems racially less fundamental, such as the adrenal or hypophysis, is incompatible with life. Profound metabolic disturbances follow the ablation of the thyroid, parathyroid, adrenal, or the hypophysis, while ovariectomy at any epoch of life produces much less striking effects upon the body economy.

Around the relatively simple, or at any rate, readily comprehensible, function of ovulation, there has been an evolutionary building-up of an intricate ancillary mechanism whose purpose is the preparation, extrusion, transport and fertilization of the egg. This mechanism is chiefly of endocrine nature, and is responsible for the intricate phenomena of the reproductive cycle. Teleologically, however, these cyclic phenomena revolve about the reproductive function, so that, from this broad standpoint, even those who no longer accept the doctrine of the "primacy of the ovum" in explaining the rhythm of menstruation will scarcely question the central importance of the egg in the phenomena of the cycle.

Before an audience of trained gynecologists and obstetricians, it is scarcely necessary to discuss the simpler aspects of the endocrinology of the cycle, though many questions are still not clear. There are few gynecologists now who are not familiar with such elementary facts as the following: (1) the rôles played by the follicle and the corpus luteum in the building-up of the endometrium from the end of one cycle to the beginning of the next; (2) the fact that these effects are due to the sequential action of estrin (folliculin) and progesterone; (3) the chronological relations of menstruation and ovulation; (4) the dependence of ovarian function upon that of the hypophysis, through the agency of the

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mammary growth and other secondary sex characters, together with a disproportionate skeletal growth like that which so characteristically follows early male castration.

As we approach puberty, the picture of the endocrine function of the ovary begins to stand out more clearly. Long before the first menstruation, maturation of follicles and production of estrin are noted, on the basis of both histologic and hormone studies. The usual sequence of events seems to be, first, incomplete maturation, then complete or almost complete maturation without ovulation but possibly with periodic bleeding, and finally full maturation, with ovulation followed by luteinization and the beginning of the usual ovulatory type of menstruation. It is as if a child, inflating a toy balloon, blows it to larger and larger size with each breath, until finally it bursts. There are certainly, however, individual time variations in the sequence of events outlined above. There can be little doubt, for example, that in many girls, ovulation begins at about the same time as menstruation, or even before, for how else could we explain the numerous cases in which pregnancy is reported to have followed immediately after the onset of the first menses, and those in which pregnancy has occurred before the first menstruation? The evidence indicates, however, that this is certainly not the invariable rule.

It can readily be shown in monkeys, for example, that anovulatory cycles are very frequent, and there is almost equally good evidence in the case of the human being. A purely follicular, anovulatory type of menstruation can be readily determined by the examination of the endometrium. In such cases the menstrual bleeding may be quite normal in amount and fairly regular in rhythm, but often there are irregularities of either amount or tempo of the flow, so that clinically such cases may present themselves as instances of functional bleeding of mild or severe grade, as the case may be.

I shall not here stop to argue the question of whether anovulatory bleeding should be included under the term menstruation, a question which has divided gynecologists into two camps, one holding that menstruation is to be defined merely as a periodic physiologic uterine bleeding, the other that it is to be limited to those cases in which ovulation occurs, a corpus luteum is formed, and certain pregravid endometrial changes thus brought about. I may emphasize, however, that the term menstruation had been used for many hundreds of years before the phenomenon was in any way linked up with pregnancy, and certainly long before the human egg or corpus luteum was discovered. Both the lay and medical concept has always been that of a normal periodic loss of blood from the genital tract, and it would seem to me illogical and unwarranted to add to this original concept the corollary that the term should be limited only to that group of cases in which ovulation occurs, even granting that this is overwhelmingly the most common type.

of puberty, and that this apparently parallels a similar awakening of pituitary gonadotropic function. It is of interest, too, to note that even in these early postnatal years, the uterus, like the fetal organ, has already acquired its selective responsiveness to the ovarian hormones, as have the breast and other secondary sex organs. This is well illustrated by the occurrence of precocious puberty and menstruation in children as a result of granulosa-cell carcinoma, as well as by the pubertal epithelial hypertrophy of the vaginal mucosa following the administration of estrogenic substances, as in the treatment of gonorrheal vaginitis.

There are still other pathologic departures that may have their origin in these early stages of ovarian development. I have already mentioned the hyperfeminization effects of granulosa-cell carcinoma, which may develop at any age, and which arises from rests of redundant granulosa left over in the early development of the oophorogenic apparatus of the ovary. In the same way, a persistence of cells of masculine proclivity, dating from the masculine scaffolding which precedes the formation of the follicular apparatus, explains the later development of the masculinizing tumors now known as arrhenoblastomas.

It seems to be true, therefore, that the initial germinal impulse is responsible for the original direction of sex differentiation, but that, as the gonads begin to function, they take over the chief burden in unfolding the secondary sex characters of the individual. While we know pathetically little about the mechanism and interrelationship of these two factors, the mere knowledge that the secondary sex phenomena are due to their interplay, and that in the human being as well as in the lower animal varying degrees of sex-reversal may occur, will enable the gynecologist to interpret his cases of intersexuality less unintelligently and less mechanistically than he might do otherwise.

He can appreciate the fact that individuals with testes may, both anatomically and psychologically, be dominantly feminine, and that others with ovaries may have many masculine characters and perhaps dominantly masculine external genitalia. He will, in short, appreciate the fact that the character of the gonad is not the only criterion in sex classification, but that chromosomal factors, with effects depending upon the embryonic age at which they become operative, are usually of much greater importance in determining sex characters. On the other hand, he can likewise appreciate why certain acquired intersexual phenomena may be explainable on a more purely endocrine basis, as in the case of cortical tumors of the adrenal or the group of sex-influencing ovarian tumors mentioned above.

Little as we know of the prepubertal function of the gonads, we do know that it must be of importance, chiefly on the basis of the negative evidence furnished by castration in early life. Observations on the female are exceedingly rare, but they indicate that the operation is followed not only by the failure of appearance of menstruation, but also of

of these cases. For the present, most of us probably content ourselves with the administration of either the anterior pituitary gonadotropic preparations or prolan substances at or near the usual time of ovulation. In one or two recent anovulatory cases receiving this treatment, a subsequent endometrial biopsy showed an undoubtedly secretory endometrium, indicating that ovulation had occurred. This evidence, however, is far from convincing, as women, like monkeys, may ovulate with some eyes and not with others.

To pass to another type of ovarian dysfunction, amenorrhea furnishes a good illustration of the multiplicity of factors which may operate to bring about the same clinical symptom, emphasizing the absurdity of the old rule-of-thumb plans of treating menstrual disorders. The three endocrine glands most frequently concerned are the ovary, the pituitary, and the thyroid, but it is not easy always to localize the primary cause, or to tell why it should occur. In the normal amenorrhea that comes with the menopause, certainly it is in the ovary that the primary break is noted, presumably as an expression of a natural limitation of the functional life span of that organ. That primary ovarian failure may occur prematurely is indicated by the occurrence of an amenorrhea which is intractable to treatment, which is accompanied by disappearance of estrin and persistence of pituitary hormone in the urine, with at times vasomotor and other subjective menopausal symptoms. The endometrium in such cases is characteristically atrophic. Such a picture would seem to leave no doubt of the primarily hypogonadal nature of the amenorrhea, constituting what is essentially a premature and almost always a permanent menopause.

As opposed to this group, there is another in which, chiefly because of the absence of any evidence of pituitary and thyroid disorder, the clinical assumption again is that the primary cause must be hypogonadal. In many of these, however, it is probable that the ovaries are capable of function were the pituitary stimulus normal. Not all cases of pituitary amenorrhea are of the adiposogenital dystrophy type, for the adiposity and other metabolic components of the Fröhlich syndrome are not due to pituitary sex hormone disorder, but to accompanying disturbance in the parhypophyseal regions of the brain, especially the hypothalamus. While the pituitary and the parapituitary disorders are usually associated, as in Fröhlich's syndrome, either one may occur without the other. Thus it is possible to have pituitary amenorrhea in patients of perfectly normal build and weight, and with normal basal rates. On the other hand, I have seen a number of patients with all the characteristics of Fröhlich's syndrome, such as the rather abrupt development of obesity of typical so-called pituitary distribution, in whom menstruation has nevertheless continued normal in amount and periodicity. Figs. 1 and 2 illustrate such a patient, whose weight had several years previously increased rather quickly from 160 to 232 pounds. The heavy shoulder

That ovulation often begins a considerable time after the onset of the menstrual function is indicated also by the clinical observation of what might be called a physiologic sterility in child brides, as has been noted in those of India. The most recent and most complete study of this sort is that of Mikulicz-Radecki and Kausch,¹ who studied a large series of young primigravidas in the Berlin Frauenklinik from the standpoint of their cohabitational histories as related to their fecundity. In a surprisingly large proportion, even though there had been an active sex life from puberty, pregnancy did not occur for from one to several years later. The obvious explanation would seem to be that the menstrual cycles for a variable though perhaps considerable time after puberty may be of the anovulatory type.

To jump to the other extreme of menstrual life, there is no doubt that in a not inconsiderable number of women approaching the menopausal age, sterility occurs because ovulation has ceased even though menstruation still proceeds, perhaps quite normally, perhaps with varying degrees of excess or irregularity, representing one grade or another of functional menorrhagia. That this is true I have been able to convince myself by endometrial biopsy studies in sterile women at this age. In other words, the age incidence of the anovulatory cycle is the same as that of the follicular type of functional bleeding, which is not surprising, since the mechanism of the two is the same, except for degree. In the distinctly abnormal cases of bleeding, the follicle not only fails to rupture, but persists abnormally long, with hyperestrinism as a result. Just as functional hemorrhage may occur at any age during reproductive life, so may the anovulatory cycle, unaccompanied by abnormal bleeding. In the detection of these cases, histologic study of the endometrium obtained just before menstruation, and usually by aspiration-curettage without anesthesia, is of crucial importance.

The question naturally arising is as to whether or not anything can be done about such cases even when they are sifted out. Unfortunately not much in the present state of our knowledge, and chiefly because we know comparatively little of the endocrine factors concerned in ovulation, though obviously they are of pituitary origin. Some believe the follicle-ripening factor the important one in ovulation, some the luteinizing factor. But the investigations of the past year or two, especially those of Hisaw and his coworkers, seem to have established that ovulation is due to neither of these factors alone, but to a delicate quantitative balance between the two. By varying the proportions of these two gonadotropic elements, these investigators have been able to induce ovulation in non-ovulating monkeys.

Unfortunately, however, it seems quite certain that the quantitative balance differs in different species, and, even more unfortunately, in different individuals of the same species, so that, from a clinical standpoint, we are faced with at least a temporary impasse in our management

of the face and extremities, in girls of perfectly normal weight and with entirely normal menstruation. Here there is a disturbance rather sharply localized in the areas and cells concerned with water and chloride balance. The fact that there is a definite menstruation-like rhythm with these extrahypophyseal cerebral disturbances is suggestive, lending support to the view, urged by Hohlweg and Junkmann² on the basis of experimental work, that behind and beyond the pituitary, as it were, there are sex centers situated in the region of the midbrain to which we must look for the explanation of many of the more fundamental characteristics of the reproductive cycle, such as its periodicity.

Such a concept, too, may help us in the explanation of such phenomena as the vasomotor symptoms of the menopause, in which both nervous and endocrine factors must be concerned. It is possibly important also in the consideration of the psychic disturbances of menstrual function and of gestation which are at times encountered. Perhaps when we know more of the nerve pathways between the sex center areas of the brain and other cerebral centers, we may be given a new understanding of segmental disturbances of fat distribution, such as those seen in lipodystrophia progressiva, in which disappearance of the subcutaneous fat in the upper part of the body and its increase in the lower part make any purely endocrine explanation almost untenable.

With reference to the relation of the thyroid to the gonads, we know comparatively little, though a relationship of some sort is indicated, not only by such clinical phenomena as menstrual swelling of the thyroid, but also by the frequency of menstrual disorders with either hypo- or hyper-function of the thyroid. The demonstration in recent years that the hypophysis, through a thyrotropic principle, dominates thyroid function, just as it does that of the ovary, has suggested to some that the thyreo-ovarian relationship may perhaps be an indirect one, mediated through the pituitary. And yet it is difficult to escape the feeling that this is not the whole story, and that the thyroid may exercise some direct influence on one or more links of the menstrual chain.

Though there is no worth-while evidence on the point, the frequent success of thyroid therapy in cases of sterility suggests that it is the germ plasm of the sex cell which may be thus affected. I have already mentioned the fact that a small proportion of normally menstruating women are sterile because they do not ovulate. There are probably a considerable number who do ovulate, but in whom the eggs are of such inferior grade that they cannot, so to speak, take the male charge. Where the germ cell inferiority is not so marked, fertilization may occur, but the resulting pregnancy "peters out" at various stages. In still others, pregnancy may continue to term, with either stillbirth or the birth of a puny infant that soon succumbs. Finally, with eggs of good quality, the initial impulse is sufficient to ensure a healthy child and normal life

pads, the large busts, the comparatively small waist, the heavy girdle of fat about the abdomen, buttocks, and hips, and the small hands and feet, all seem characteristic of the Fröhlich type; and yet the pituitary sex hormones are apparently functioning quite normally, as indicated by the normal menstrual function.

It is this cerebral type of obesity which is so difficult to treat with any success, and which, as I pointed out in a recent paper, is at times associated with disturbance of the water balance. In a certain group of cases, the course of the condition may be marked by remarkable weight in-

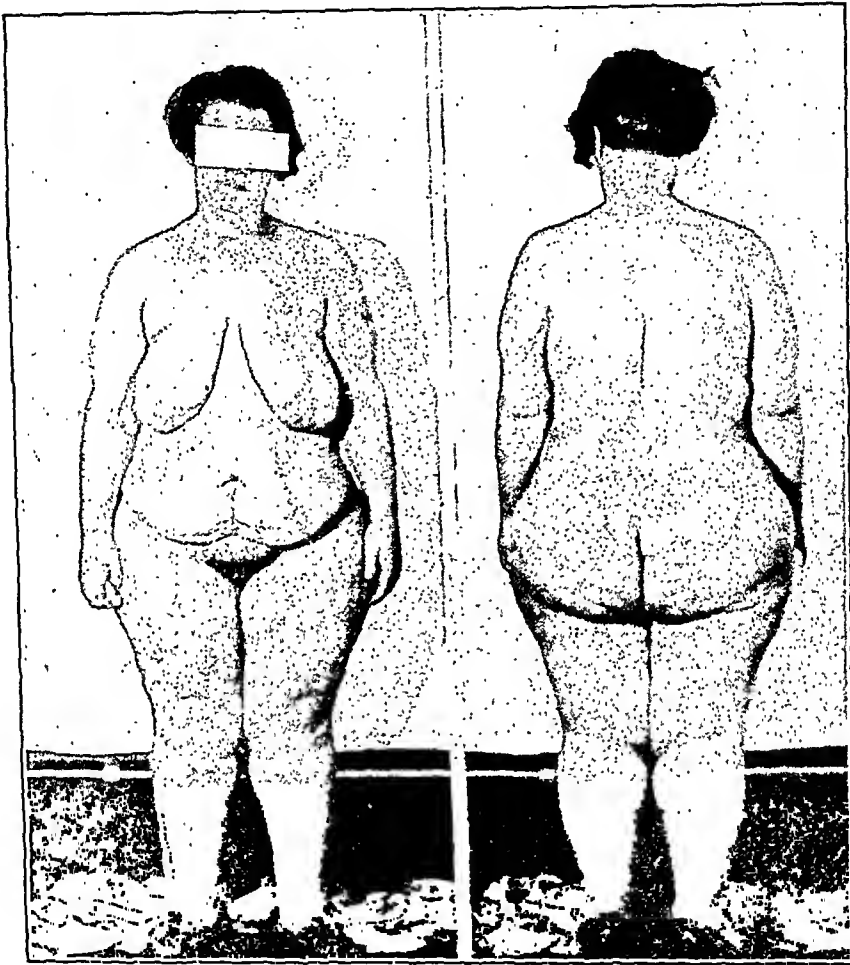


Fig. 1.

Fig. 2.

Fig. 1.—Patient, aged twenty-six years, had increased in weight rather abruptly from 160 to 222 pounds, the distribution of fat being of so-called "hypopituitary" type, but menstruation was normal in every respect.

Fig. 2.—Posterior view of patient shown in Fig. 1.

creases during menstruation, with rapid drop after the period, accompanied often by polyuria. To add to the confusion, and to illustrate further how we must try to differentiate the results of disturbances in this region on the basis not of organs but of individual centers, one may encounter menstrual edema in girls who are not obese and whose menstrual function is normal. I have seen menstrual edema, with a gain of even fifteen pounds during the periods, and with very evident swelling

the synthetic process is as yet practical from a commercial standpoint, for such is not the case, but it does make it very probable that such methods are reasonably sure to come in the not very distant future.

From the standpoint of medical science in general, one of the most provocative of all the discoveries in this rich field has been that a close chemical affinity exists between the estrogenic substances and certain well-known carcinogenic substances, particularly the tar derivatives. Certain of the latter are definitely estrogenic, while a considerable amount of evidence has already been accumulated to indicate that the estrogenic substances under certain conditions may be carcinogenic. This is a long story in itself, and I have summarized it in a recent paper with Yui.⁵ In this paper we have also presented some evidence to suggest the carcinogenic tendencies of estrin upon the endometrium of women beyond the menopause.

An interesting development of recent years has been the frequent finding of estrin in the urine of women long after the menopause, and even long after surgical castration. This would seem to preclude the possibility of the ovaries as a source of the estrogenic principle. Whether estrin production may be assumed by some other endocrine organ after removal of the ovaries, as is done by the placenta during pregnancy, or whether the postmenopausal estrin is a chemical metabolite of some sort, we cannot say.

Our own study, based on the review of 864 cases of hyperplasia, showed this lesion to be not very rare in women well beyond the menopause, this observation checking with the occasional finding of estrin in the urine of elderly women, as above mentioned. Our study included a review of 104 cases of adenocarcinoma of the fundus during the same eleven-year period, with the disclosure that the noncancerous endometrium in this group showed a disproportionately high incidence of hyperplasia, even though the women were well beyond the menopause.

The inference would seem justified, therefore, that a postmenopausal endometrium subjected to persistent estrogenic stimulation is predisposed to adenocarcinoma. This observation is in accordance with Loch's conclusion, after a thorough review of the problem, that estrogenic substances have been demonstrated to be carcinogenic in those tissues and organs which are normally under the physiologic control of estrin. This would apply especially to the uterus and the breast. In the latter organ the long-continued injection of estrin has apparently produced cancer in a surprising proportion of cases, and the malignant process thus initiated has run its usual course even after the hormone has been withdrawn. Cancerlike pictures have been produced in the same way in the cervix, although, so far as I know, none of these lesions has continued after hormone administration has been stopped.

Such observations have opened up an entirely new lead in cancer investigation, and one which is sure to yield interesting results regardless

expectancy. This factor of defective germ plasma as a cause of sterility and "idiopathic" miscarriage is now accepted by all embryologists (Streeter),³ and there is some reason to believe, chiefly on the basis of the frequent value of thyroid therapy in such cases, that it is this factor which is influenced by the thyroid.

In this connection I may call attention to a very recent study made by Young and Blandau⁴ upon guinea pigs. This investigation was directed to determining the relationship between the age of the ovum and the course of gestation and development. As might be expected in view of other studies, the percentage of impregnations following insemination decreases as ovum age (after ovulation) increases, the extreme limit of ovum viability being found to be twenty-six hours. Of chief interest, perhaps, was the high incidence of embryonic death noted when the older ova are fertilized. In the guinea pig, therefore, it would seem that defects in the ovum due to its age may be an important cause of miscarriage. The suggestion would be that other defects of germ plasma might likewise be responsible for abnormalities of embryonic development, and quite probably in human beings as well as in the lower animals.

There are many other aspects of ovarian dysfunction which invite discussion, and most of them have important practical bearings upon clinical problems, such as dysmenorrhea, sterility, habitual abortion, menopausal symptoms, gonorrheal vaginitis in children, etc., but it would obviously be impossible to discuss them all within the limits of a paper of considerate length. One other subject, however, I cannot refrain from touching upon, because it constitutes the most important recent development in gynecologic endocrinology. I refer to the new knowledge which has been gained concerning the chemistry of the sex hormones, the demonstration of the chemical kinship of the two ovarian hormones, one with another, and also with the male sex hormone. I shall go into no detail on this subject, especially as I have reviewed it in a recent paper.

Even more interesting, perhaps, has been the revelation that the structural formula of all these hormones is similar to that of certain well-known chemical substances of the sterol group, and that estrous phenomena can be elicited in castrated animals by the injection of these non-hormonal chemicals as well as by the estrogenic hormones themselves. A tremendous impetus has been given to the chemical study of the whole group of estrogenic substances, and many derivatives have been described, with marked differences in the degree of estrogenic potency. The possibility of synthetic preparation of estrogenic substances, as well as of progesterone, has become a very real one. Already, for example, it has been possible to synthesize progesterone from pregnenolone, a substance found in the urine of pregnancy, whereas the only source hitherto has been the corpus luteum itself. This does not, of course, mean that

THE ETIOLOGY AND TREATMENT OF PRIMARY DYSMENORRHEA*

A PHYSIOLOGIC AND CLINICAL STUDY

JULIUS E. LACKNER, M.D., LEON KROHN, M.D., AND
SAMUEL SOSKIN, M.D., CHICAGO, ILL.

*(From the Department of Gynecology and Obstetrics and the Department of
Metabolism and Endocrinology of Michael Reese Hospital)*

THE multiplicity of factors involved in dysmenorrhea has given rise to many conflicting theories as regards its etiology, none of which have supplied a completely adequate explanation. It is not our purpose, at the present time, to review in detail the ideas advanced by Novak and Reynolds,¹ Kennedy,² Israel,³ and others. Suffice it to say that the recent advances in the field of endocrinology have directed attention to the endocrine aspects of dysmenorrhea and it is from this point of view that primary or functional dysmenorrhea is now generally regarded.

It is well established that the estrogenic substances augment, and that progesterone decreases the motility of the uterus, in various laboratory animals. Similar observations have been made by Falls, Lackner and Krohn⁴ on the puerperal human uterus. The present authors have recently demonstrated that the same applies to the normal nonpregnant and nonpuerperal human uterus.⁵ In view of these facts it would seem logical to conclude, as Novak and Reynolds¹ have done, that the pain in primary dysmenorrhea is due to an exaggerated contractility of the uterus, consequent to a faulty balance of the above hormones at the menstrual period. Mohr,⁶ who recorded the uterine contractions in a patient suffering from severe dysmenorrhea, carried the analogy between uterine pain and pain in other muscular organs, a step farther. He observed that the sensation of greatest discomfort coincided with the peak of each contraction, and that each peak was marked by a disappearance of the arterial pulsation, which was superimposed on the other portions of his graphic record. He, therefore, suggested that the pain in dysmenorrhea might be associated with a relative ischemia of the uterus, as has been supposed to occur in the heart with angina pectoris, and in the skeletal muscle with intermittent claudication.

Another endocrine theory of dysmenorrhea has been advanced by Kennedy,² who believes that it is associated with degenerative changes in Frankenhauser's ganglion, as a result of a deficiency of estrin. Aside

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of whether or not they bring us closer to the solution of cancer etiology. This new application of endocrinology to the problems of human disease is but another of the many developments which justify the early hopes and enthusiasm of those who were farsighted enough to interest themselves in the subject in its earlier days, when the ductless gland enthusiast, however honest and earnest, was looked upon with condescension, if not derision, because of the motley crew of pseudoscientific ragamuffins and commercialists who crowded under the same banner. Within the short period of a quarter of a century, the tone of endocrinology has been immeasurably elevated, in spite of rapid advances which would almost excuse immoderate enthusiasm. No more brilliant chapter has been added to the scroll of medical science than that contributed by endocrinologists, and yet the wisest and most conservative among them all agree that only the surface has as yet been scratched, and that what has already been accomplished merely foreshadows even richer possibilities in the future. Small wonder, therefore, that anatomists, physiologists, and chemists have manifested such widespread interest in endocrine research, and that more and more clinicians, especially the younger men of our profession, have come to appreciate the indispensability of endocrinology in the everyday interpretation of clinical problems.

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26 EAST PRESTON STREET

Gray, Laman A.: Lymphogranuloma Inguinale of the Female Urethra, Surg. Gynec. Obst. 62: 745, 1936.

Eleven cases of this disease affecting the female urethra are reported. The disease presents a syndrome consisting of: a chronic urethritis, with or without intraurethral ulceration, which may remain extremely chronic and indolent or may proceed to urethral stricture, or to ulcerative destruction of the urethra; an ulceration which may extend beneath the clitoris and labia, or around the introitus and deeply to the sides of the rectum; and possibly an associated elephantiasis vulvae.

The presence of positive Frei reactions in 9 of the 11 cases indicates that this syndrome is probably due to the virus of lymphopathia venereum, "lymphogranuloma inguinale."

A wide variety of parenteral and local treatments had no appreciable influence on the disease. Two patients with least treatment showed the greatest healing. The indications are that cure, as in other virus diseases, probably depends on immunity.

WM. C. HENSKE.

from the opposing theoretical considerations involved in this and the theory outlined above, the two hypotheses present a practical conflict in therapeutics. If one is to act on the belief that dysmenorrhea is caused

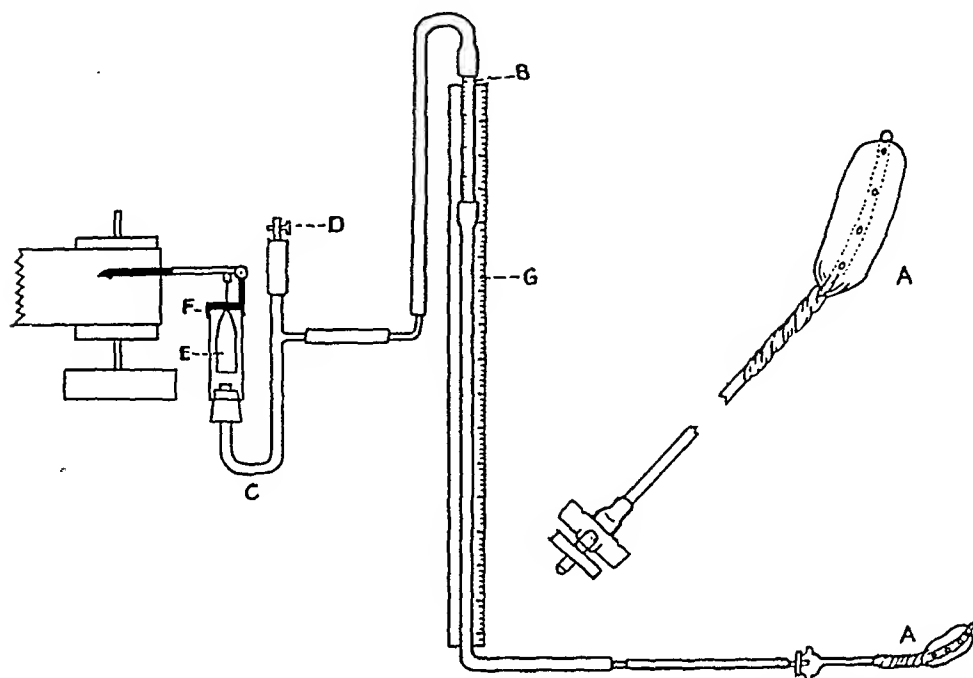


Fig. 1.—Apparatus for recording uterine motility at known volume and pressure. (A) Balloon ensemble, (B) calibrated leveling tube, (C) water manometer, (D) stopcock, (E) Balsa-wood float, (F) metal cap supporting the recording lever, and (G) movable scale.

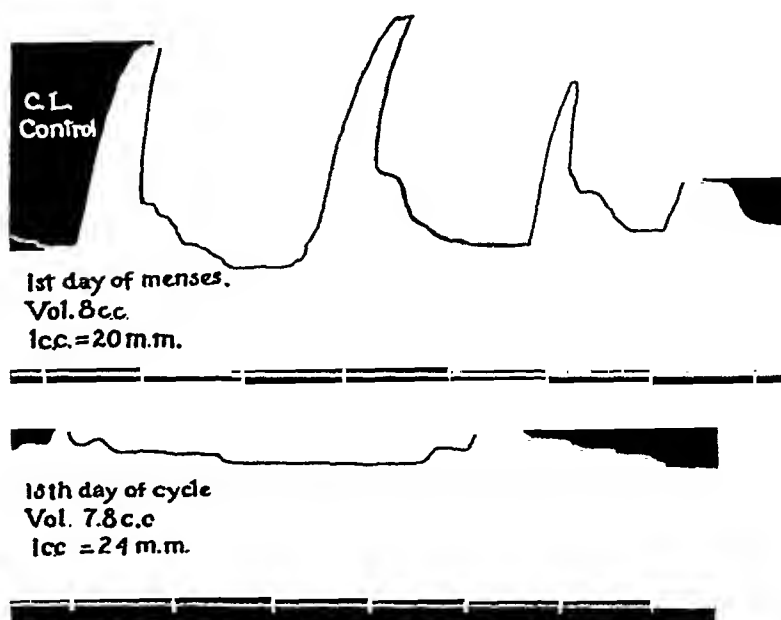


Fig. 2.—Uterine motility in a normal control on the first and fifteenth days of the menstrual cycle. Photographic reduction $4\frac{1}{2}$ times.

by an exaggerated contractility of the uterus due to a relative preponderance of estrin, the logical treatment is the administration of progester-

TABLE I. SUMMARY OF RESULTS

TABLE 1. SUMMARY OF RESULTS

CASE	DIAGNOSIS	FIRST DAY OF MENSES BEFORE TREATMENT					PAIN	TREATMENT	UTERINE CONTRACTIONS	UTERINE ENDOMETRIUM	URINE		BLOOD	
		UTERINE CONTRACTIONS	UTERINE ENDOMETRIUM	ESTRIN		ESTRIN					PROLAN			
				FREE	COMBINED									
C. L.	Normal	Very large	Cervical epithelium and glands	30	120	-	0	0			<30			
M. G.	Normal	Moderate	Secretory	30	30	-	0	0						
H. W.	Normal	Large	Hyperplastic	30	30	-	0	0						
P. G.	Normal	Large	Proliferative	120	120	+	0	0						
E. R.	Primary dysmenorrhea	Large	Proliferative	180	180	+	Progesterone	Relieved	Moderate	Secretory	<30	30	-	-
M. Gu.	Primary dysmenorrhea	Very large	Early secretory			+	Progesterone	Relieved	Very large	Early secretory			-	-
E. S.	Primary dysmenorrhea	Large	Atrophic	<30	30	-	Progesterone	Relieved	Large	Proliferative	<30	30	-	-
M. W.	Primary dysmenorrhea	Very large	Secretory	<30	30	-	Progesterone	Relieved	Moderate	Secretory	<30	<30	+	-
G. L.	Primary dysmenorrhea	Large	Secretory	<30	<30	-	Progesterone	Relieved	Moderate	Early secretory	<30	30	-	-
K. W.	Primary dysmenorrhea	Large	Secretory	<30	<30	-	Estrogenic substance	Relieved	Moderate	Hyperplastic	30	30	-	-
N. M.	Primary dysmenorrhea	None	Insufficient	60	60	-	Estrogenic substance	Relieved	Small	Late proliferative	120	180	+	-
P. Gi.	Primary dysmenorrhea	Small	Proliferative	30	60	-	Estrogenic substance	Relieved	Moderate	Insufficient	30	60	-	+
G. N.	Primary dysmenorrhea	Large	Hyperplastic	30	60	-	Progesterone	No relief	Large	Late proliferative	120	120	+	-
E. A.	Primary dysmenorrhea	Large tetanic	Hyperplastic	120	120	-	Progesterone	No relief	Large	Proliferative	<30	<30	-	-
E. A.	Primary dysmenorrhea	Large tetanic	Hyperplastic	120	120	-	Estrogenic substance	Slight relief	Large	Proliferative	<30	30	-	-

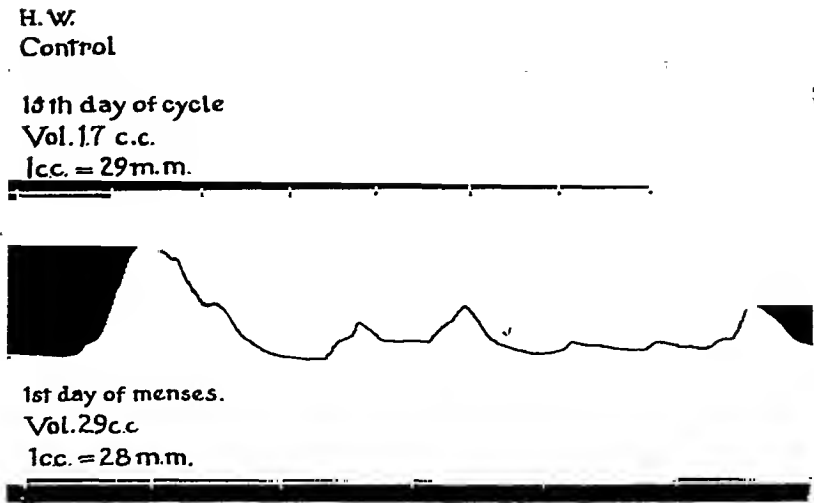


Fig. 4.—Uterine motility in a normal control on the first and fifteenth days of the menstrual cycle. Photographic reduction 3 times.

TABLE IV. CASE H. W., AGED THIRTY-NINE, PARA 0. CONTROL

	MIDPERIOD	FIRST DAY OF MENSES
Volume of uterus	1.7 c.c.	2.9 c.c.
Contractions	None	Large, fairly regular About 1 per minute
Blood	Prolan, minus Estrin, minus	Prolan, minus Estrin, minus
Urine estrin	Free 30 Combined 30	Free 30 Combined 30
Endometrium	Insufficient	Hyperplastic

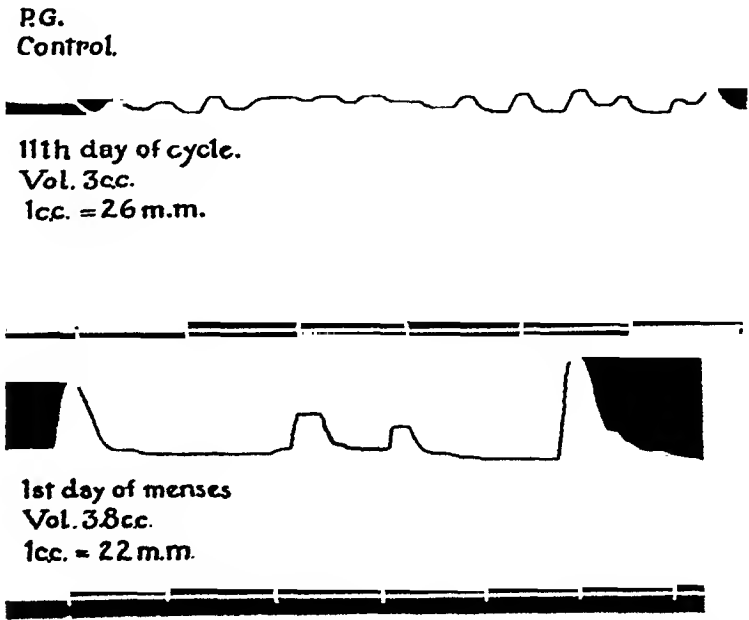


Fig. 5.—Uterine motility in a normal control on the first and eleventh days of the menstrual cycle. Photographic reduction 3 1/2 times.

TABLE II. CASE C. L., AGED TWENTY-ONE YEARS, PARA II. CONTROL

	MIDPERIOD	FIRST DAY OF MENSES
Volume of uterus	7.8 c.c.	8.0 c.c.
Contractions	Small, irregular	Very large, regular 1 every 2 minutes
Blood	Prolan, minus Estrin, minus	Prolan, plus Estrin, minus
Urine estrin	Free < 30 Combined < 30	Free 30 Combined 120
Endometrium	Proliferating	Cervical epithelium and glands

one, as applied by Campbell and Hisaw,⁷ and Elden and Wilson.⁸ Or, an increase in available progesterone in the individual may be secondarily induced by the administration of the luteinizing principle of pregnancy urine, as advocated by Novak and Reynolds,¹ Browne,⁹ and

M.G.
Control

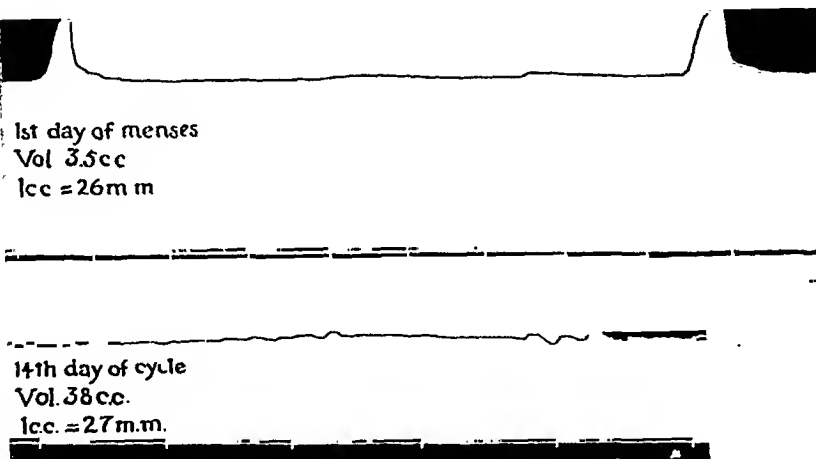


Fig. 3.—Uterine motility in a normal control on the first and fourteenth days of the menstrual cycle. Photographic reduction $3\frac{1}{2}$ times.

TABLE III. CASE M. G., AGED TWENTY-THREE, PARA I. CONTROL

	MIDPERIOD	FIRST DAY OF MENSES
Volume of uterus	3.8 c.c.	3.5 c.c.
Contractions	Small, irregular	Moderate, regular 1 every five minutes
Blood	Prolan, minus Estrin, minus	Prolan, minus Estrin, minus
Urine estrin	Free < 30 Combined 60	Free 30 Combined 30
Endometrium	Proliferating	Secretory

Witherspoon.¹⁰ According to this view the administration of estrogenic substance would actually aggravate the dysmenorrhea. Whereas, if one accepts the views of Kennedy, estrogenic substance is the treatment of choice.

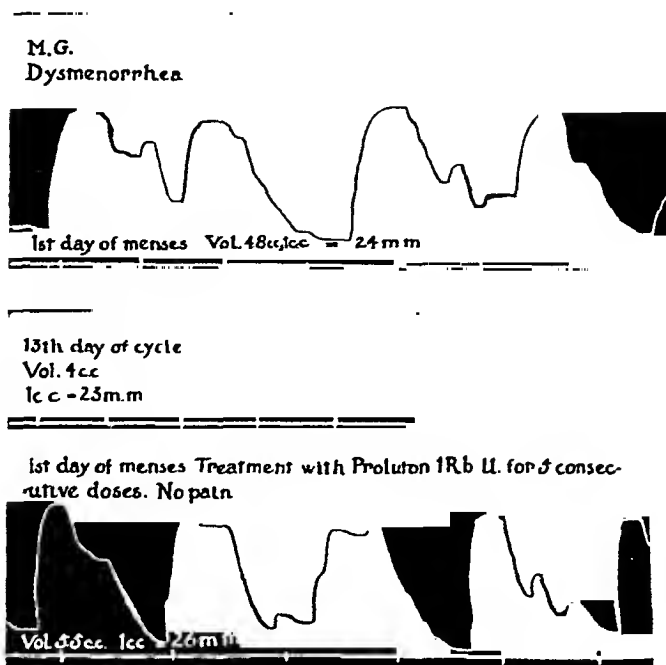


Fig. 7.—Uterine motility in a patient with dysmenorrhea on the first and thirteenth days of the menstrual cycle before treatment, and on the first day of menstruation after treatment with progesterone. Photographic reduction 4 times.

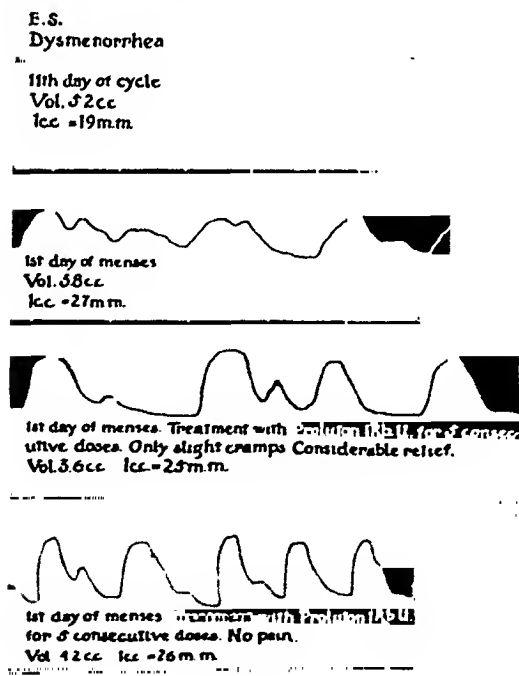


Fig. 8.

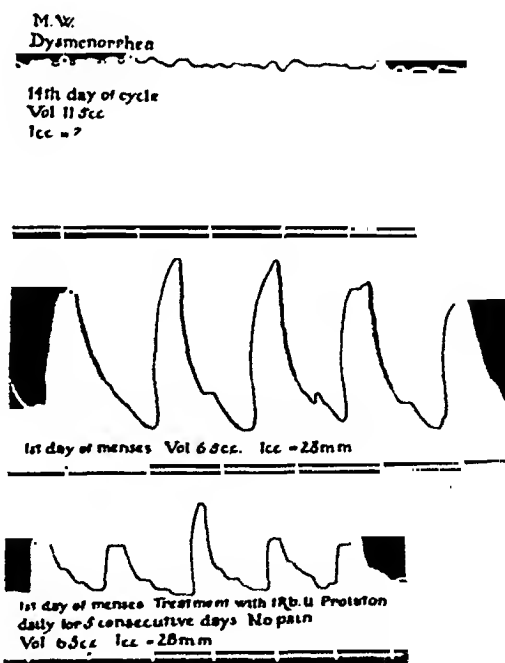


Fig. 9.

Fig. 8.—Uterine motility in a patient with dysmenorrhea on the first and eleventh days of the menstrual cycle before treatment, and on the first day of menstruation after treatment with progesterone. Photographic reduction 4 times.

Fig. 9.—Uterine motility in a patient with dysmenorrhea on the first and fourteenth days of the menstrual cycle before treatment, and on the first day of menstruation after treatment with progesterone. Photographic reduction 5 times.

TABLE V. CASE P. G., AGED THIRTY-FIVE, PARA II. CONTROL

	MIDPERIOD	FIRST DAY OF MENSES
Volume of uterus	3.0 c.c.	3.8 c.c.
Contractions	Small, fairly regular 2 per minute	Large, fairly regular 1 every 2 minutes
Blood	Prolan, minus Estrin, plus	Prolan, minus Estrin, plus
Urine estrin	Free 60 Combined 120	Free 120 Combined 120
Endometrium	Proliferative	Proliferative

It appeared to us likely that the two mechanisms described in the above hypotheses were not mutually exclusive, but that each of them, and perhaps other factors, operated in different groups of patients. It there-

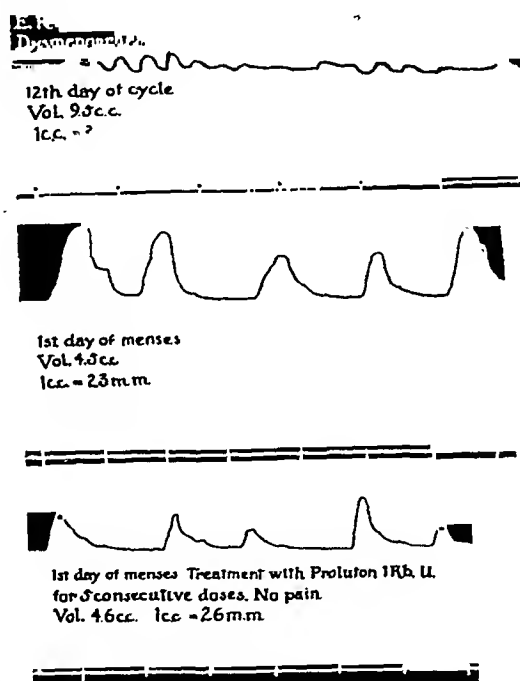


Fig. 6.—Uterine motility in a patient with dysmenorrhea on the first and twelfth days of the menstrual cycle before treatment, and on the first day of menstruation after treatment with progesterone. Photographic reduction 3 times.

TABLE VI. CASE E. R., AGED TWENTY-ONE, PARA I. DYSMENORRHEA

	MIDPERIOD	FIRST DAY OF MENSES	FIRST DAY OF MENSES SUBSEQUENT TO TREATMENT WITH PROGESTERONE
Pain	None	Severe	None
Volume of uterus	9.5 c.c.	4.5 c.c.	4.6 c.c.
Contractions	Small, 2-3 per minute	Large, 1-1½ minutes apart	Moderate 1-1½ minutes apart
Blood	Prolan, minus Estrin, plus	Prolan, minus Estrin, plus	Prolan, minus Estrin, minus
Urine estrin	Free 120 I.U. Combined 120 I.U.	Free 180 I.U. Combined 180 I.U.	Free < 30 I.U. Combined 30 I.U.
Endometrium	Insufficient	Proliferative	Secretory

PROCEDURE

The nature of the methods which we employed precluded the possibility of a statistical study on a large number of patients. Instead, a small group of women suffering from primary dysmenorrhea and a few normal women were studied as intensively and as objectively as possible. Graphic records of uterine motility, biopsies of the uterine endometrium, and hormone assays of the blood and urine were made simultaneously in each subject, at certain intervals. In four normal women these observations were made at the midperiod and on the first day of menstruation. In ten dysmenorrheic women these observations were made at the midperiod, on the first day of menstruation when pain was present, and on the first day of a subsequent menstrual period or periods after the patient had received endocrine therapy.

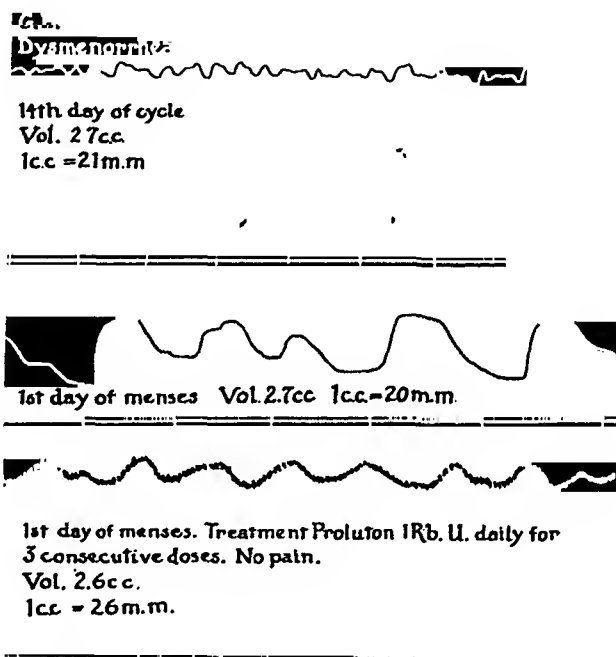


Fig. 10.—Uterine motility in a patient with dysmenorrhea on the first and fourteenth days of the menstrual cycle before treatment, and on the first day of menstruation after treatment with progesterone. Photographie reduction 4 times.

TABLE X. CASE G. L., AGED THIRTY, PARA 0. DYSMENORRHEA

	MIDPERIOD	FIRST DAY OF MENSES	FIRST DAY OF MENSES SUBSEQUENT TO TREATMENT WITH PROGESTERONE
Pain	None	Moderately severe	None
Volume of uterus	2.7 c.c.	2.7 c.c.	2.6 c.c.
Contractions	Small, fairly regular, 2-3 per minute	Large, fairly regular, 1 per minute	Moderate, regular 2 per minute
Blood	Prolan, minus Estrin, minus	Prolan, minus Estrin, minus	Prolan, minus Estrin, minus
Urine estrin	Free < 30 Combined 30	Free < 30 Combined < 30	Free < 30 Combined 30
Endometrium	Early secretory	Secretory	Early secretory

fore seemed important to study a number of women suffering from primary dysmenorrhea with a view to differentiating the various types of

TABLE VII. CASE M. Gu., AGED TWENTY-ONE, PARA I. DYSMENORRHEA

	MIDPERIOD	FIRST DAY OF MENSES	FIRST DAY OF MENSES SUBSEQUENT TO TREATMENT WITH PROGESTERONE
Pain	None	Severe	None
Volume of uterus	4 c.c.	4.8 c.c.	5.5 c.c.
Contractions	None	Very large. Regular. 1 every 2 minutes	Very large, regular 1 every minute
Blood	Prolan, minus Estrin, minus	Prolan, minus Estrin, plus	Prolan, minus Estrin, minus
Urine estrin	Free < 30 Combined < 30		
Endometrium	Late prolifera- tive	Early secretory	Early secretory

TABLE VIII. CASE E. S., AGED TWENTY-FOUR, PARA 0. DYSMENORRHEA

	MIDPERIOD	FIRST DAY OF MENSES	FIRST DAY OF MENSES SUBSEQUENT TO TREATMENT WITH PROGESTERONE
Pain	None	Very severe	Slight discomfort
Volume of uterus	5.2 c.c.	3.8 c.c.	4.2 c.c.
Contractions	None	Large, regular 1 per minute	Large, regular 1 per minute
Blood	Prolan, plus Estrin, plus	Prolan, minus Estrin, minus	Prolan, minus Estrin, minus
Urine estrin	Free 60 Combined 60	Free < 30 Combined 30	Free < 30 Combined 30
Endometrium	Proliferative	Atrophic	Proliferative

TABLE IX. CASE M. W., AGED TWENTY-SIX, PARA I. DYSMENORRHEA

	MIDPERIOD	FIRST DAY OF MENSES	FIRST DAY OF MENSES SUBSEQUENT TO TREATMENT WITH PROGESTERONE
Pain	None	Moderately severe	None
Volume of uterus	11.5 c.c.	6.5 c.c.	6.3 c.c.
Contractions	Irregular, small 3 per minute	Very large, regular 1 per minute	Moderate, regular 1 per minute
Blood	Prolan, minus Estrin, minus	Prolan, minus Estrin, minus	Prolan, minus Estrin, plus
Urine estrin	Free 45 Combined 45	Free < 30 Combined 30	Free < 30 Combined < 30
Endometrium	Proliferative	Secretory	Secretory

cases, and with the hope of establishing criteria by which they might be distinguished from each other.

Endometrial biopsies were obtained with Novak's suction curette.¹¹ To make sure of getting a true picture of the entire endometrium, we took several strips from different parts of the uterus (Figs. 16 to 19).

The acetone precipitation¹² and tungstic acid precipitation¹³ methods respectively, both previously reported from this laboratory, were used to assay the estrogenic and gonadotropic hormones in the blood samples, and the free and total estrin in the twenty-four-hour urine specimens. The gonadotropic hormone in the urine was not estimated since it is known to parallel that in the blood.¹⁴ In the assay of blood estrin the test was called positive when the extract from 40 c.c. of blood produced a cornified smear in a castrated mouse in forty-eight to sixty hours, signifying at least 25 mouse units per liter. The test for gonadotropic hormone in the blood was considered positive when the extract from 40 c.c. of blood produced an Aschheim-Zondek reaction in twenty-three- to twenty-five-day-old rats, in one hundred hours.

N.M.
Dysmenorrhea

1st day of menses
Vol. 17cc
1cc = ?

9th day of cycle
Vol. 17cc
1cc = ?

1st day of menses Treatment with Progynon B
No pain
Vol. 19cc 1cc = ?

Fig. 12.—Uterine motility in a patient with dysmenorrhea on the first and ninth days of the menstrual cycle before treatment and on the first day of menstruation after treatment with estrogenic substance. Photographic reduction $3\frac{1}{2}$ times.

TABLE XII. CASE N. M., AGED TWENTY-NINE, PARA 0. DYSMENORRHEA

	MIDPERIOD	FIRST DAY OF MENSES	FIRST DAY OF MENSES SUBSEQUENT TO TREATMENT WITH ESTROGENIC SUBSTANCE
Pain	None	Severe	None
Volume of uterus	1.7 c.c.	1.7 c.c.	1.8 c.c.
Contractions	None	None	Small, irregular 1-2 per minute
Blood		Prolan, minus Estrin, minus	Prolan, minus Estrin, plus-plus
Urine estrin		Free 60 Combined 60	Free 120 Combined 180
Endometrium	Insufficient	Insufficient	Late proliferative

The methods used for the above purposes have been described in detail in another communication.⁵ Briefly summarized they are as follows:

Uterine motility was recorded, at a known intrauterine pressure and volume, by means of a rubber balloon inserted into the uterus, and connected through a calibrated leveling device to a new type of recording water manometer (Fig. 1). In connection with the use of the sterilized rubber balloon in the uterus it may be of interest to note that, in approximately eighty tests, we have experienced practically no difficulty as regards its insertion or withdrawal. Preliminary dilatation of the cervix has never been necessary. The one case of relative stenosis of the cervix which we encountered was in an apparently normal woman, who did not complain of dysmenorrhea. The presence of the balloon in the uterus occasionally caused slight discomfort, but in no instance have we observed after-effects of any kind.

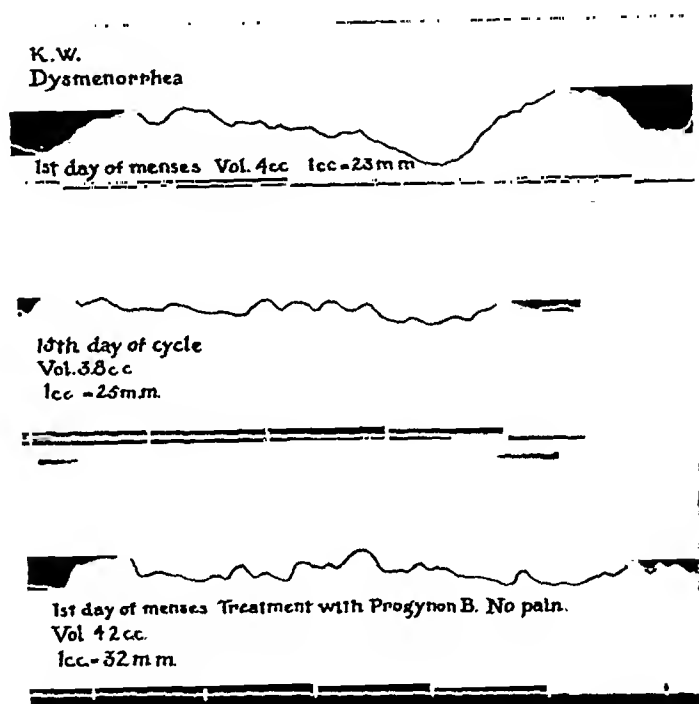


Fig. 11.—Uterine motility in a patient with dysmenorrhea on the first and fifteenth days of the menstrual cycle before treatment, and on the first day of menstruation after treatment with estrogenic substance. Photographic reduction 4 times.

TABLE XI. CASE K. W., AGED THIRTY-FOUR, PARA 0. DYSMENORRHEA

	MIDPERIOD	FIRST DAY OF MENSES	FIRST DAY OF MENSES SUBSEQUENT TO TREATMENT WITH ESTROGENIC SUBSTANCE
Pain	None	Severe	None
Volume of uterus	3.8 c.c.	4 c.c.	4.2 c.c.
Contractions	Small, fairly regular. 3 per minute	Large, irregular occasionally tetanic	Moderate, irregular 2 per minute
Blood	Prolan, plus Estrin, plus	Prolan, minus Estrin, minus	Prolan, minus Estrin, minus
Urine estrin	Free 30 Combined 240	Free < 30 Combined < 30	Free 30 Combined 30
Endometrium	Secretory	Secretory	Hyperplastic

In all the motility records which are presented the recording pressure was 100 cm. of water, and the time markings on the base-line represent one-minute intervals.

DISCUSSION

We should like to forestall any misapprehension by being the first to disclaim that we have solved the etiology and treatment of primary dysmenorrhea. However, the least equivocal and perhaps the most practically important of our results, is the fact that we have been able to give complete relief to eight out of the ten dysmenorrheic women whom we attempted to treat with endocrine preparations. It need hardly be pointed out that these gratifying therapeutic results cannot be called "cures," since the treatment is substitutional rather than curative in

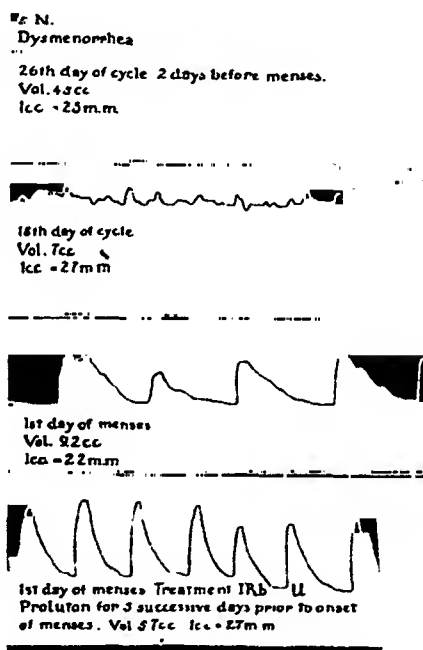


Fig. 14.—Uterine motility in a patient with dysmenorrhea on the first, fifteenth and twenty-sixth days of the menstrual cycle before treatment, and on the first day of menstruation after treatment with progesterone. Photographic reduction 6 times.

TABLE XIV. CASE G. N., AGED THIRTY-ONE, PARA III. DYSMENORRHEA

	MIDPERIOD	FIRST DAY OF MENSES	FIRST DAY OF MENSES SUBSEQUENT TO TREATMENT WITH PROGESTERONE
Pain	None	Severe	Severe
Volume of uterus	7 c.c.	9.2 c.c.	5.7 c.c.
Contractions	Small, irregular 2 per minute	Large, regular 1 per minute	Large, regular 1 per minute
Blood	Prolan, plus Estrin, plus	Prolan, minus Estrin, minus	Prolan, minus Estrin, plus
Urine estrin	Free 60 Combined 120	Free 30 Combined 60	Free 120 Combined 120
Endometrium	Secretory	Hyperplastic	Late proliferative
Therapy with estrogenic substance at a subsequent period gave slight relief.			

The urine estrin figures, for purposes of record, have been converted from mouse units into international units which are given in our tables. In our laboratory 1 mouse unit equals 3 international units.

RESULTS

The results in each experimental subject are briefly noted in an individual tabulation (Tables II to XV) accompanied by a corresponding set of illustrative records of uterine motility (Figs. 2 to 15). Much of the data in these tables we have found difficult of correlation and interpretation, at the present state of our knowledge. These have been included for future reference and in the hope that others, from a different viewpoint, may perhaps be able to read more into them than we have. Such data, from all the above tables, as have seemed to us to have immediate significance in the interpretation of our results, have been summarized in Table I for purposes of comparison.

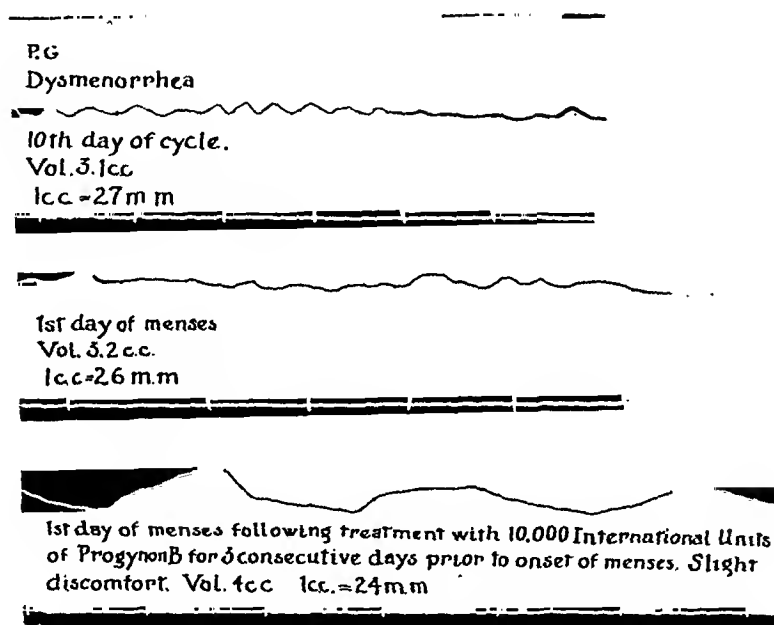


Fig. 13.—Uterine motility in a patient with dysmenorrhea on the first and tenth days of the menstrual cycle and on the first day of menstruation after treatment with estrogenic substance. Photographic reduction $3\frac{1}{2}$ times.

TABLE XIII. CASE P. Gi., AGED TWENTY-EIGHT, PARA 0. DYSMENORRHEA

	MIDPERIOD	FIRST DAY OF MENSES	FIRST DAY OF MENSES SUBSEQUENT TO TREATMENT WITH ESTROGENIC SUBSTANCE
Pain	None	Severe	None
Volume of uterus	3.1 c.c.	3.2 c.c.	4 c.c.
Contractions	Small, fairly regular, 3 per minute	Small, irregular spasms 2 per minute	Moderate, prolonged regular 1 every 2 minutes
Blood	Prolan, minus Estrin, minus	Prolan, plus Estrin, minus	Prolan, plus Estrin, minus
Urine estrin	Free < 30 Combined < 30	Free 30 Combined 60	Free 30 Combined 60
Endometrium	Insufficient	Proliferative	Insufficient

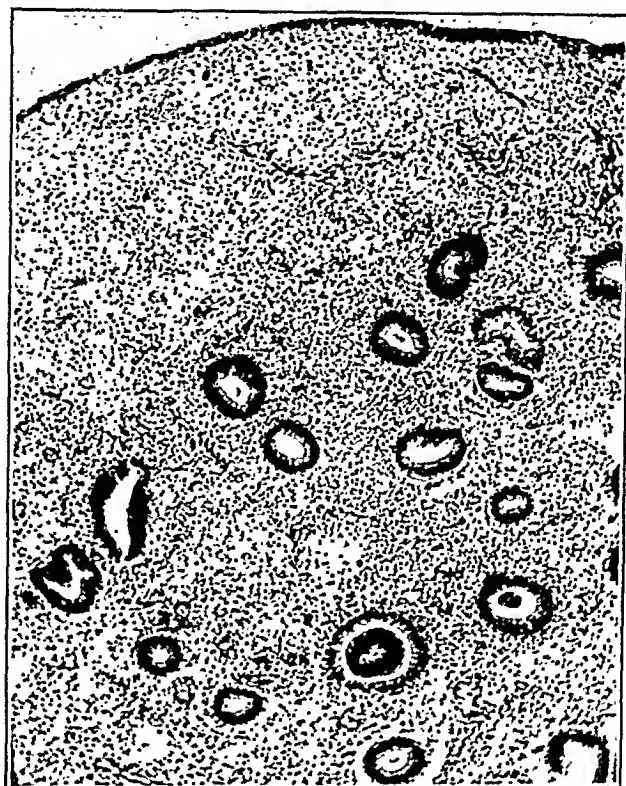


Fig. 16.—Early proliferative endometrium ($\times 75$). The thickness of the endometrium is 1.1 mm. The glands are few and straight. The epithelium is of low columnar type. The nuclei are centrally located. The stroma is loose.



Fig. 17.—Late proliferative endometrium ($\times 75$). The thickness of the endometrium is approximately 2 mm. The glands are increased in number with beginning convolution. The epithelium is unchanged.

nature. Nevertheless, these results confirm the view that primary dysmenorrhea is largely of endocrine origin, and have at least enabled us to draw some negative conclusions as to the mechanism of the pain in dysmenorrhea, as outlined below.

On the basis of our results, the 10 patients whom we treated may be divided into 3 groups. Five were completely relieved by progesterone, 3 by estrogenic substance, while 2 patients obtained little or no relief

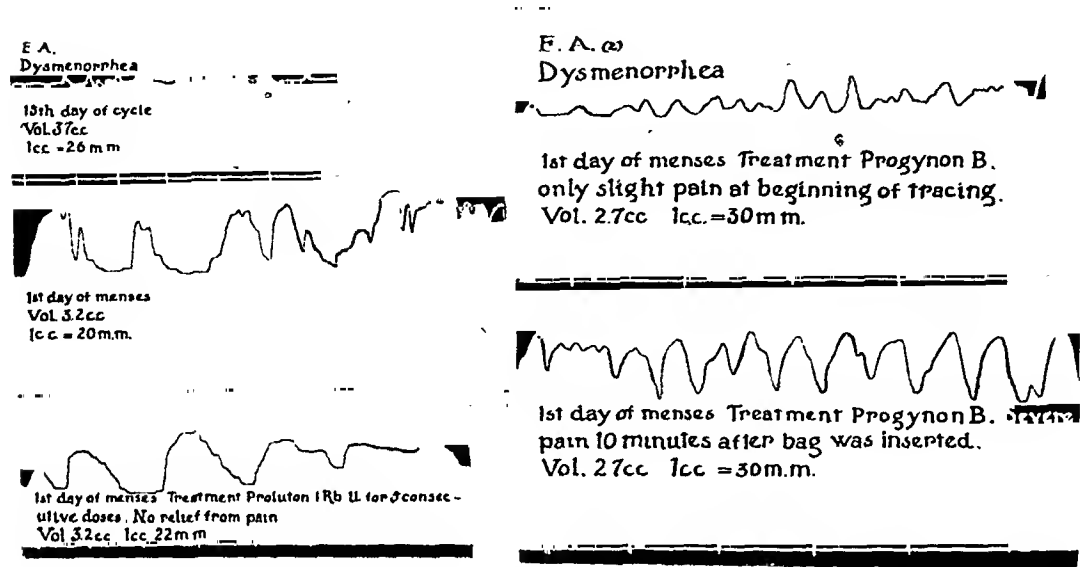


Fig. 15.—A, Uterine motility in a patient with dysmenorrhea on the first and fifteenth days of the menstrual cycle before treatment and on the first day of menstruation after treatment with progesterone. Photographic reduction 4 times. B, Uterine motility in the same patient on the first day of menstruation after treatment with estrogenic substance. Photographic reduction 3 times.

TABLE XV. CASE E. A., AGED TWENTY-FIVE, PARA 0. DYSMENORRHEA

	MIDPERIOD	FIRST DAY OF MENSES	FIRST DAY OF MENSES SUBSE- QUENT TO TREATMENT WITH PROGESTERONE	FIRST DAY OF MENSES SUBSE- QUENT TO TREAT- MENT WITH ESTROGENIC SUBSTANCE
Pain	None	Very severe	Severe	Moderate
Volume of uterus	3.7 c.c.	3.2 c.c.	3.2 c.c.	2.7 c.c.
Contractions	Small irregular	Large tetanic irregular	Large, fairly regular, 1 every 2 minutes	Small, fairly regu- lar, about 3 per minute at first. After 10 minutes large, regular, 2 per minute
Blood	Prolan, minus Estrin, minus	Prolan, minus Estrin, minus	Prolan, minus Estrin, minus	Prolan, minus Estrin, minus
Urine estrin	Free 45 Combined 180	Free 120 Combined 120	Free 30 Combined 30	Free < 30 Combined 30
Endome- trium	Slight atrophy	Early pro- liferative	Proliferative	Proliferative

from either form of therapy. This distribution of results apparently confirms our prediction as to the validity, in different groups of patients, of both the hypotheses mentioned in our introductory remarks. In addition to these two types of dysmenorrhea, however, there is apparently a third type in which the mechanism is not restored to normal by either of the endocrine preparations which we used.

In none of the above groups of cases were we able to correlate strictly any of our experimental observations with the occurrence of pain, although certain tendencies were obvious. Thus, in most of the patients, large uterine contractions were recorded at the time during which pain was experienced. Furthermore, the greatest intensity of the pain usually coincided with the peak of each contraction. Nevertheless, similarly large uterine contractions were observed in normal women who never complained of dysmenorrhea; and, what is perhaps of greater significance, at least two of the women treated with progesterone showed no diminution in the size of their uterine contractions at the time that their pain was completely relieved. It is true that the other three cases treated with progesterone exhibited a decrease in the size of their uterine motility coincident with the disappearance of pain. The difference between these and the above cases may depend on the dose of the hormone which they received relative to their needs. But, at any rate, it is apparent that symptomatic relief can be produced by doses of progesterone which are less than the amount necessary to cause a demonstrable decrease in the uterine contractions. In the face of these results it would be difficult to maintain that the pain in dysmenorrhea is directly related to the intensity of the uterine contraction, even if one were to invoke the variations in the "pain threshold" as suggested by Novak and Reynolds.¹ As regards the suggestion of Moir,⁶ that the pain is related to ischemia of the uterine muscle, we have been unable to confirm his observation upon which this idea was based. In some of our cases, the arterial pulsation superimposed on the motility record persisted throughout the peaks of the contractions.

Our other experimental data showed even less direct correlation with the uterine pain than did the size of the uterine contractions. This applies alike to the frequency of the uterine contractions, to the state of the uterine endometrium, and to the titer of the hormones in the blood and urine. This is not to say that the endometrium and the hormone assays did not correspond in some cases with the grouping of the case as regards the presence of a relative preponderance of progesterone or of estrogenic substance. The difficulty rests on the fact that the same endometrial and hormonal findings were also present in certain cases which fell into opposing groups as far as the response to therapy was concerned.

It is clear that our efforts to discover the actual cause of the pain in dysmenorrhea must be extended to other channels and methods. Our

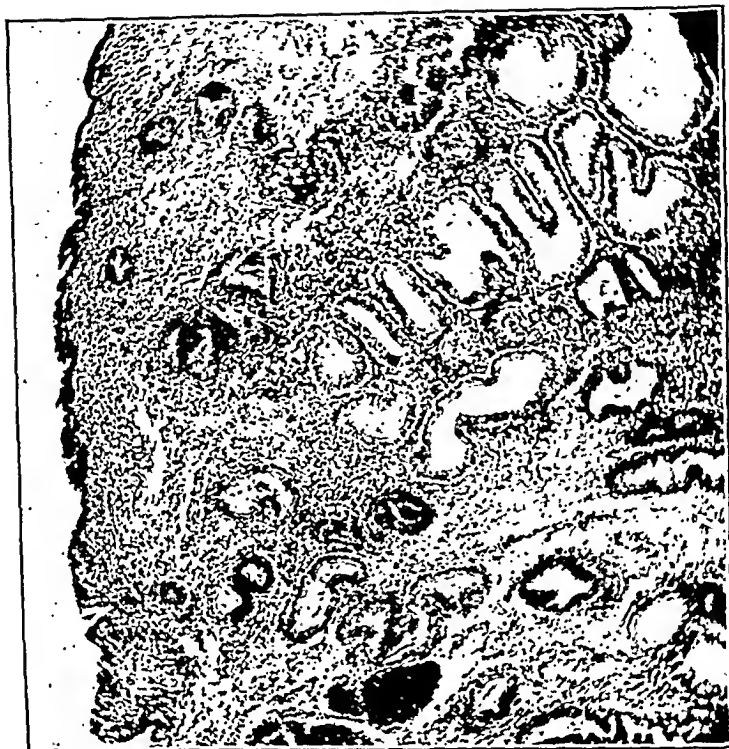


Fig. 18.—Early secretory endometrium ($\times 75$). The thickness of the endometrium is 3 to 3.5 mm. The glands are the same in number but are now moderately convoluted. The epithelium is of tall columnar type and the nuclei are located at the base.



Fig. 19.—Late secretory endometrium ($\times 75$). The thickness of the endometrium is approximately 4 mm. The glands are typically corkscrew, dilated, and filled with secretion. The epithelial borders are frayed. The cells are packed with vacuoles. The stroma is condensed.

Regarding the experiments we should know how long a foreign body can be retained in the uterus without causing irritation. Most of the curves represent only four contractions extending over a few minutes. It is important to know what a longer curve would show. In the first control, for example, the first contraction is very high, the second high, the third low, and the fourth not quite so low. Therefore even in four consecutive contractions, there is a wide variation. It is very difficult, as they have stated already, to correlate the different curves. Finally, the curves presented are too few to permit conclusions. I should like to have these authors continue with their work and present a list of 100 controls.

DR. KROHN (closing).—It is true that only a small number of controls are included in this report. This was because of the extreme difficulty encountered in securing normal women willing to lend themselves to this type of study.

The slides we demonstrated were photographs of a typical section of the original tracings of the uterine motility. The kymographic records were very long, since we usually allowed the intrauterine bag to remain in place for from two to three hours. The contractions on each individual record did not vary a great deal. In the normal control cases, the volume of the uterus seemed to be in direct proportion with the size of the uterine contractions. That is, large contractions were recorded from patients with a large uterine volume and when the uterine volume was small, the contractions were correspondingly small.

Lepontre, C.: Pyelitis of Defloration, *Bull. Soc. d'obst. et de gynéc.* 25: 701, 1936.

The author reports his experience with pyelitis which follows defloration. The pyelitis in these cases has been attributed to infection which results from rupture of the hymen and also to trauma at the urethral orifice during attempts at coitus in women who have a high perineum and a narrow vaginal introitus. These cases are often erroneously attributed to a gonorrheal infection transmitted by the husband. The consequences of such an error may be very serious. The mistake may be avoided by examining the urine microscopically, for only colon bacilli will be found.

In the discussion of this paper Delannoy took exception to the name pyelitis of defloration. He attributes this pyelitis to a change in the manner of living of young married people and the fatigue of a honeymoon, and hence he thinks a better term is pyelitis of the honeymoon.

J. P. GREENHILL.

Ch'in, T. L., and Lim, K. T.: The Yeast-Like Fungi Found in the Vagina of Pregnant and Non-Pregnant Women, *Chinese M. J.* 50: 1211, 1936.

The authors made 200 vaginal cultures, 100 from pregnant and 100 from non-pregnant women. Among the pregnant cases there were 39 patients positive for yeasts, while in the nonpregnant cases there were 11. In the pregnant cases the yeasts were more frequently found in young women, and also in the latter part of pregnancy. This difference is most probably due to a higher glycogen content in the vaginal mucosa of pregnant women, a condition favoring the growth of yeasts and promoting the formation of an acid medium unfavorable to most bacterial organisms.

C. O. MALAND.

results, fruitless in this regard, have nevertheless yielded information of some practical importance. Thus the dysmenorrheic patient with a large, well-developed uterus which exhibits moderate to large contractions, usually obtains complete relief from pain after treatment with progesterone. The patient with the small hypoplastic uterus, which shows little or no contraction, is likely to respond favorably to estrogenic substance. Using these simple criteria for the proper selection of cases, it should be possible completely to relieve a large proportion of the women who regularly suffer from this common and disabling form of pain.

CONCLUSIONS

1. Eight out of ten women, suffering from primary dysmenorrhea, have been completely, though temporarily, relieved by endocrine therapy. This form of dysmenorrhea may therefore be regarded as being largely of endocrine origin.

2. The patients whom we studied and treated may be divided into three groups: Those who were relieved by progesterone, those who responded to estrogenic substance, and those in whom neither of these substances was effective.

3. We have been unable to establish any strict correlation between the occurrence of menstrual pain and of uterine contractions, the state of the uterine endometrium, or the hormone content of blood and urine.

4. Certain simple and general criteria have been outlined to aid in the proper selection of cases for treatment with progesterone and estrogenic substance respectively.

NOTE.—We are indebted to Dr. Gregory Stragnell of the Schering Corporation for ample supplies of progynon B and proluton; to Dr. Otto Saphir for generous cooperation with the histologic interpretations; and to Dr. S. Charles Freed for the performance of the arduous task of assaying many samples of blood and urine for their hormone content.

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DISCUSSION

DR. JEAN PAUL PRATT, DETROIT, MICH.—The chief value of the contribution is found in the attempt to establish a causal relation for hormonal therapy. Yet the authors have wavered a little in their interpretation. In evidence of this is their third conclusion: "We have been unable to establish any strict correlation between the occurrence of menstrual pain and of uterine contractions, the state of uterine endometrium, or the hormone content of the blood and urine." They answer their own question about the fallibility of endocrine therapy.

The time relationship between the most recent pregnancy and the development of the chorionepithelioma is subject to wide variations. Coincident with intrauterine pregnancy were the cases reported by Walthard, Gustavson, Eyding (1933), Stoeckl (1933), Jacob (1930), and most recently by Davis and Brunshwig (1936). Coexisting with an intrauterine mole were the cases of Halter (1930), Schiebele, Sunde, Lehmann (cited by Halter, 1930), and Pantshenko (1931). Appearance of the tumor after the menopause has been reported by Koritschoner (de Zalka, 1928), Kroesing, McCann, Devitzky, and Polano (Ries, 1913). Feiner (1935) analyzed a number of these reports. Well-authenticated cases following a long latent period are rare in the recent literature.

Chorionepithelioma follows moles, abortions, term pregnancies and ectopic pregnancies in the order mentioned. In this, as in many other phases of this study, individual reports differ. Polak (1931) stated that in ten years he had seen 40 or 50 moles, none of them malignant, and in the same interval, 10 chorionepitheliomas without antecedent mole history. Larger series indicate that 50 per cent are preceded by moles, the others develop after term pregnancies and abortions with a slight emphasis on the latter. The high incidence of malignancy following mole, 5 per cent or more, indicates the gravity of this condition. In 1934 a total of 36 chorionepitheliomas of the fallopian tubes and an equal number of the ovary had been reported. The ectopic form has been studied carefully by Findley (1904), de Zalka (1928), and Sears (1933).

The pathology of chorionepithelioma is essentially an intensification or exaggeration of many of the growth processes of normal pregnancy. The normal chorion is a rapidly proliferating tissue with definite invasive qualities and a tendency to metastasize. When malignant, these functions are exaggerated, and diagnosis rests on the recognition of such hyperplasia. Chorionepithelioma arises from the cells of the fetal trophoblast. Both the Langhans' layer and the syncytium are involved, but rarely to the same degree. Numerous attempts have been made to classify these tumors on the basis of cellular constituents, but none of these classifications has clinical application although Ewing's seems best. Since both types of cells have a common origin there is no need of precise distinction. Predominance of either type of cell in a tumor cannot be relied on as an infallible criterion of malignancy. Recognition of the distortion of the normal processes, not always easy, is most important. Erroneous diagnoses have been made often, leading either to fatal procrastination or to unnecessary sacrifice of pelvic viscera.

The uterine tumor may consist of only a few cells or it may fill the entire pelvis. It is a hemorrhagic growth due to the invasion of blood vessels. There is no stroma, hence, no intravillous vessels, and the cells in the deeper parts of the tumor grow away from their blood supply. Both necrosis and hemorrhage thus result. The lesion may lie super-

A STUDY OF FIVE PATIENTS WITH CHORIONEPITHELIOMA*

JAMES A. GOUGH, M.D., CHICAGO, ILL.

(From the Department of Obstetrics and Gynecology, St. Luke's Hospital)

CHORIONEPITHELIOMA when originally described by Saenger in 1889 was considered decidual in origin and designated "sarcoma uteri deciduocellulare." By 1895 several other reports had been published, among them those by Williams and Marchand. The latter correctly ascribed the origin of the cellular elements to the fetal trophoblast and introduced the name now in use. During the next thirty years many isolated case reports were published. Much of this is difficult to evaluate because, as a rule, only in rare instances did the author observe more than one case. The novelty of the diagnosis also may have resulted in publications not entirely acceptable to more critical readers.

The pitfalls in histologic diagnosis were recognized by most observers, but no test was available which would substantiate or refute the impression aroused by the microscope. In 1928 Aschheim and Zondek, on the basis of hormone studies, offered a test for determining pregnancy which has enhanced the methods for detecting the presence of chorionepithelioma. Today the histologic structure of tissues is supplemented by this test in diagnosis.

A few of the published statistics indicate both the rarity and irregular appearance of cases of chorionepithelioma. Kimbrough (1934) observed the disease twice in 8,335 confinements, Winter (1934), three cases among 8,000. Schwalm (1934) stated that in twenty-two years no patients with the disease were observed at the Berlin Charité Frauenklinik, while Eymer (1932) at the Heidelberg Frauenklinik collected nine in twenty years. St. Sommer (1934) in Prague found one in ten years among 18,000 confinements, Joravieff (1933) in the Soviet Union reported one in 26,000.

Chorionepithelioma occurs usually in multiparas. In Teacher's series the youngest patient was seventeen, the oldest fifty-five, and the average age of the group was thirty-three years. The disease occurred during the first pregnancy in only 5 per cent of this series, following the second and third in 28 per cent. Vineberg (1919) quoted Briquel's figures indicating an incidence of 47 per cent in the fourth pregnancy. In v. Szathmary's analysis (1930) of 500 patients with chorionepithelioma, the average age was thirty-four years, and 4.4 pregnancies preceded the onset; in one-third of this group the condition developed after forty in women who had had eight pregnancies. Gestations late in the childbearing period are more likely to terminate as moles, hence, the higher incidence of chorionepitheliomas in this group. Devitzky's patient (Ries, 1913) at seventy-five seems to be the oldest on record. Cases occurring in early childhood are teratomatous like the testicular type.

*Read at the Eighth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Detroit, Mich., October 15 to 17, 1936.

an observation which seems to have no parallel in published reports. These few instances serve only to emphasize the rarity of primary lymphatic involvement. The so-called chorionepithelioma testis metastasizes through the lymphatic system, suggesting a fundamental difference in type of tumor even though the cellular elements and biologic reactions may be indistinguishable.

As a rule, the persistence of bleeding following an abortion or the expulsion of a mole is the most common clinical symptom, and further bleeding after a curettage is almost pathognomonic. Too often, however, the microscopic examination of this material is neglected or when made does not reveal its true nature, in fact, even the myometrium of the excised uterus will often show no more than regions of necrosis and blood extravasation. The circumscribed lesion deep in the myometrium, obviously, is inaccessible to the curette. Pain is variable, and as a rule develops late in the disease; anemia usually is in proportion to the blood loss, and by increasing the operative hazard as well as lowering resistance to infection constitutes the most serious symptom. Low-grade fever, due to bacterial invasion of the uterus through a patulous cervix, is common, and severe sepsis often has prevented radical excision or caused death.

Metastatic lesions, due to their hematogenous origin, are intimately associated with the blood vessels of the tissues involved, and the symptoms they produce result from bleeding or other vascular phenomena, such as bleeding varies in the vaginal wall, hematuria, hemoptysis, etc. Cerebral lesions are frequently characterized by symptoms of increased intracranial pressure or by cranial nerve involvement.

Many patients are not observed long enough, and the development of symptoms due to metastases has finally called attention to the true nature of the condition. The seriousness of this omission has been stressed particularly by Curtis (1932). Presenting the greatest difficulties in diagnosis are the tumors which occur in the puerperium when physiologic bleeding masks the symptoms of the malignant growth, so strikingly illustrated in the reports by Lull (1935) and Winter (1934).

The hormone studies, especially the Aschheim-Zondek test and its modifications, are invaluable in the study of chorionepithelioma. So important is this test that skepticism regarding many of the older reports is aroused, particularly those recording spontaneous cures and diagnoses based entirely on the microscopic examination of curetted material. Similar reports today would be made with reluctance except when substantiated by biologic tests, because the presence of living chorion in any part of the body is manifested by the excretion of excessive quantities of anterior pituitary-like hormone. In normal pregnancies an error of 1 or 2 per cent occurs in these tests, and at

ficially on the endometrium, within the myometrium, or project into the peritoneal cavity as a subserous mass. Some tumors have a superficial hyperplasia, while others are best exemplified by the so-called invasive mole, in which the first symptoms may be peritoneal or those due to uterine rupture. Anspach and Hoffman (1931) have reported such a tumor and have reviewed the records, citing nine other well-authenticated cases.

Histologically there are: an active hyperplasia and accumulation of the covering elements of the villi, both Langhans' layer and the syncytium; penetration of both these elements deep into the wall of the uterus; numerous Langhans' cells in mitosis; and regions of necrosis and hemorrhage. All of these conditions may not be present in the sections examined, and sometimes hemorrhage and tissue destruction dominate to the exclusion of finer details.

Chorionepithelioma in women has a decided tendency to metastasize through the blood stream, and lesions in the vaginal wall and lungs are usually the first to appear when dissemination occurs. This, of course, is a natural sequence, because the chorion even in normal pregnancy invades the uterine vessels, and, as Schmorl many years ago stated, benign embolic chorionic tissue can be demonstrated in distant viscera in fully 80 per cent of pregnancies. These facts are important in treatment. Unless there is gross evidence of extension into the parametrium, the dissection during a hysterectomy need not be as wide as when done for carcinoma, and the knowledge that pulmonary metastases may appear first should be a guide in deciding the operability of a patient and the subsequent treatment. Moreover, the blood vessel metastases urge gentleness in manipulating the uterus, as emphasized by Hitschmann.

Vaginal metastases are interesting features of this disease. This unique retrograde metastasis is attributed to anastomoses between the uterine vessels and those of the anterior vaginal wall. In about half of the patients, according to Williams, a vaginal metastasis is the first symptom. The lesions usually occur near the urethral meatus, vary from a few millimeters to several centimeters in diameter, appear superficial, are blue in color, and resemble varices. When traumatized, they bleed freely. This accident often has led to a diagnosis of the basic disease. Stroganova (1931) questioned the importance of this lesion and stated that he had observed it in other conditions. In my patients no vaginal metastases occurred.

Exceptions to the hematogenous type of dissemination have been observed.

Cases have been reported by Lutfi and Schükri (1933), who cite similar observations by Riesel and Kroemer, in which lymphatic involvement has been conspicuous. Ikeda and Ikeda (1933) report a patient with generalized involvement of the skin,

the physician. Further confusion is caused by variation in the degree of malignancy, some tumors appearing almost benign in their response to minor or inconsequential treatment, others produce death before their nature is suspected. The factors, apart from trauma, actually functioning in producing embolic metastases also are unknown.

A marked improvement in prognosis has resulted from the use of the Aschheim-Zondek test. In contrast with the previous mortality of 60 per cent or more is the report by Engelhart (1935). He observed five consecutive patients in the last eight years in all of whom the diagnosis and treatment were controlled by this test, and all were returned to good health. Similar reports are becoming more common.

In patients with chorionepithelioma following pregnancies not of the mole type, failure to make an early diagnosis may be fatal to the patient but this is not a reflection on the attending physician. Prolonged or repeated bleeding following a confinement or abortion, however, should prompt a hormone test of the urine, and a wider use of the latter will aid in decreasing the mortality. Hydatidiform mole should be considered a potentially malignant tumor. The various criteria advanced for differentiating benign from malignant moles, while of interest, in no manner refute the simple fact that the malignant mole, regardless of its structure, precedes chorionepithelioma. The age of the patient bearing the mole may be more important than the histologic structure.

This is clearly illustrated by v. Szathmary's analysis. Under forty, mole preceded chorionepithelioma in 37.7 per cent with a mortality of 40 per cent; at age forty and over, a preceding history of mole was obtained in 68 per cent, and the death rate had mounted at forty to 74 per cent, at fifty to more than 80 per cent. This increased incidence of malignancy of the chorion in patients approaching the climacterium coincides with the same tendency in other pelvic tissues at this age. While in younger women anxious to bear children a more conservative attitude can be taken, the diagnosis of mole in a patient past forty years of age should indicate hysterectomy.

When chorionepithelioma has been diagnosed, prompt complete excision of the tissues involved is the ideal treatment. Anemia should be combated by transfusion before the operation. Abdominal hysterectomy is the operation of choice, permitting better exposure, the ligation of vessels before clamping and cutting, and the removal of the uterus with the least trauma, as well as assuring better hemostasis. The lutein cysts of the ovary are due to the disease and have no causative significance, hence, removal or conservation of the ovaries is optional. The excision of tissue-containing malignant cells, however, would naturally take precedence over the conservation of ovarian function. The cervix should, of course, be removed.

There are relatively few reports in English of primary irradiation in the treatment of chorionepithelioma, its use being restricted largely to inoperable cases or to those with metastases.

times nonpregnant women may excrete an excessive amount of the hormone. Controversy arises when the histologic structure and the Aschheim-Zondek test do not coincide.

The report of Fahlbusch (1930) is an example. The histologic diagnosis was made by Robert Meyer; the Aschheim-Zondek test, however, was negative and continued thus. No treatment was given after the curettage and the patient remained well. Mathieu and Palmer (1935) advance as a very rational explanation of these apparent discrepancies that the first urine specimen was obtained five days after the operation, and in both of their patients the Friedman test had become negative by that time. Further experience will clarify similar conflicting statements.

The biologic test should be valued, but the absence or presence of an excessive quantity of the hormone in a single specimen of urine should not outweigh clinical judgment. A repeatedly positive reaction without other symptoms has demonstrated the great value of this test (Leventhal and Saphir, 1934), and a single negative report does not exclude malignancy. Chorionic cells which develop malignant tendencies after a period of latency must have survived, and their presence may be obscured by an occasional inconsistent result. Such a variation in the intensity of the hormone reaction was shown in the patient recently reported by Garber and Young (1936), in whom chorionepithelioma developed five months after an hydatidiform mole, meanwhile two of the Friedman tests were only weakly positive. Similarly in the fourth patient of my group, all of the reactions were less strongly positive in the interval between the abortion of the mole and the hysterectomy. Persistence of a positive reaction, even though it is slight, is far more suggestive than a single one with high hormone content.

Blindly accepting the fact that the test often remains positive for several months after the expulsion of a mole (Aschheim, 1930) may lead to disaster, again illustrated by the fourth patient in my report. Malignancy seemed to be present in the chorion of the original mole, and so marked were these in the material of the second curettage that hysterectomy was urged although less than six weeks had elapsed. This opinion was substantiated by the sections which show well-developed chorionepithelioma metastasis in the myometrium.

In no other disease is prognosis dependent so much on early recognition and early treatment. An abnormal type of pregnancy by its nature warns the physician of serious sequelae, and hormone tests are done on the slightest suspicion. But when physiologic chorion becomes malignant during an otherwise uneventful pregnancy or puerperium, recognition may come too late. Numerous factors serve to overwhelm the patient, such as the confusion of symptoms with those due to the pregnancy, the anemia and lowered resistance, the tendency to metastasize through the blood stream and the dilated pelvic vessels favoring embolism. The result depends on factors beyond the control of

larly each month. There had been no other pregnancies. The urine contained 5 mg. of albumin per 100 c.c. On Dec. 27, 1929, the supravaginal portion of the uterus and the appendix vermiformis were removed by Dr. Barrett.

The uterus amputated through the cervix 2 to 3 cm. below the internal os was 7.5 cm. long. It had been split to the cavum lengthwise in the posterior mid-sagittal plane. Near the vertex on the anterior wall, closely attached, was a tough gray tissue with small vesicles 2.2 by 2.0 cm. elevated 0.7 cm. In the muscle beneath were several other vesicles 7 to 8 mm. in diameter. In the anterior wall toward the right cornu another section had been made down to the mass mentioned, and in this tract was a vesicle 2.2 by 1.5 by 1.7 cm. At the periphery, a channel 5 to 6 mm. in diameter extended to the amputation of the broad ligament. Dr. Barrett stated that another vesicle had been found in this sinus, and, in fact, a collapsed structure 1.2 cm. in diameter was present. The wall of the uterus in its posterior mid-sagittal plane was 1.8 cm. thick, and 1 mm. of this was hyperemic lining. The lining of the upper part of the cervix had the usual arbor vitae markings.

Sections were cut so as to include the myometrium and the mass of tissue adherent to the lining surface. The muscle contained several large blood vessels with

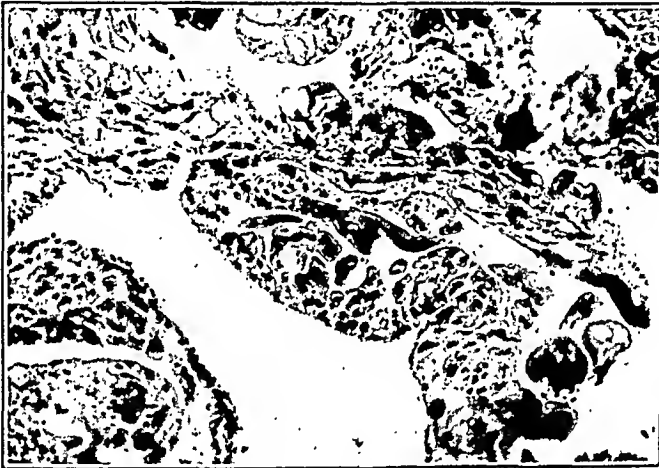


Fig. 1.—Photomicrograph of a metastasis in the lumen of a blood vessel. $\times 212$

thick walls surrounded by a zone of fibrous tissue. About some of the blood vessels were small collections of lymphocytes and a few polynuclear leucocytes. The mass protruding into the cavum was continuous with the dense fibrous tissue and large blood vessels. It had a fibrous stroma and a variety of large swollen cells, some resembling huge decidua cells; bizarre chorionic villi with a compact fibrous stroma, Langhans' cells and syncytial cells. There was a hyperplasia of the syncytium into irregular multinuclear protoplasmic masses. In the lumen of a large blood vessel, as seen in Fig. 1, were masses of these syncytial cells, and large solitary cells had penetrated the intima and media of some of the blood vessels.

The patient recovered promptly from the operation and has remained well. The Aschheim-Zondek tests to date have been negative.

CASE 2.—M. W., a negress, aged twenty-three years, entered the hospital on the service of Dr. H. O. Jones on Nov. 19, 1929. She was married at the age of fourteen, and had been delivered twice, seven and six years before. The last menstrual period was April 24, 1929; during the latter part of June there had been slight vaginal bleeding, and on the first of July she aborted spontaneously. From then until admitted there had been a slight continuous bleeding. There were moderate secondary anemia, a temperature of 99.6° F., and a pulse of 108 per minute when she

The excellent results obtained by Davis and Brunschwig (1936), Lackner and Leventhal (1932), Beach (1934), and Thomas (1934) indicate the value of this form of therapy. The German literature is more voluminous and contains a number of excellent reports, some authors having used x-ray alone and others combining it with radium. Wintz's (1931) report is particularly impressive; of 9 patients, all considered serious, treated by irradiation alone, 7 were cured. Gál (1933) lists the advantages of irradiation therapy as the avoidance of bleeding, infection, and the mechanical dissemination of metastases. Certainly in the inoperable patient and when the surgical risk is great, irradiation has proved valuable. Further experience may justify an extension of this form of treatment.

The following five reports are the records of the only cases of chorionepithelioma observed at St. Luke's Hospital, Chicago. Among the case histories of this institution there are two more in which the diagnosis clinically and histologically justifies their inclusion, but inability to make further contact with these patients has necessitated their omission. It will be noted that the diagnosis had not been made prior to 1929, but during the following year two cases were observed and since then three more have been studied. Since these occurrences coincide with what may be called a transition period in the diagnosis of this disease, a recital of our case histories will illustrate the value of the Aschheim-Zondek test.

The tissue examinations were made by Dr. Edwin F. Hirsch, Attending Pathologist at St. Luke's Hospital. The finer discriminations in histologic structure essential in the diagnosis of this condition are not within the province of the clinician.

The biologic tests were made by Dr. William Tate, Jr., using the modification of the original Aschheim-Zondek technic described by Davis and Ferrill (1932). Albino rats twenty-five to thirty days old and weighing 40 to 50 gm. were used. The test may be made with either male or female animals, but in this series females were used exclusively. Four intraperitoneal injections of 2 c.c. of urine were given at twelve-hour intervals, and the animals sacrificed forty-eight to seventy-two hours later. This technic has been entirely satisfactory in the routine performance of pregnancy tests. The quantity of urine used is somewhat larger than is necessary to elicit a reaction in normal pregnancy, but the reading is easily made and is attended by only a small error. From an economic standpoint, in the avoidance of questionable reactions, and for the greater detail obtained in his studies of early pregnancies, Dr. Tate prefers rats to either mice or rabbits.

CASE HISTORIES

CASE 1.—F. De J., a white woman aged thirty-eight years and married for one year, had been well until four months before entering St. Luke's Hospital Dec. 26, 1929. After several weeks of amenorrhea and sudden metrorrhagia, her physician, Dr. C. W. Barrett, in August, 1929, had curetted the uterus and discovered an hydatidiform mole. There were no symptoms for a month and then bleeding recurred. It was slight but almost constant; menstruation, however, occurred regu-

6,050 per c.mm., and the hemoglobin was 52 per cent. On March 20, 1930, four months after the curettage, and nine months after the abortion, the supravaginal portion only of the uterus was removed.

The upper 6 cm. of the uterus including 3 cm. of the cavum had been cut to the lumen in the mid-sagittal plane (Fig. 2); the wall here was 3.3 cm. thick, and of this, 3 mm. was endometrium. The peritoneum was smooth and glistening. Intramural in the vertex was a circumscribed mass of tissue 4.5 by 3.5 by 4.5 cm., which, on surfaces made by cutting, contained several large dark red blood clots. In some respects it resembled an extremely hemorrhagic fibromyoma, but the fibrous-like stroma formed a porous framework with tissue spaces about 1 cm. in diameter filled with blood clots. The histologic preparations contained many red blood cells and fibrin, and, as shown in Fig. 3, chorionic villi covered with irregular masses of syncytium. The tissue structure was that of a chorionepithelioma.

The patient was discharged from the hospital on April 17, 1930. On May 18, there was a small hemorrhage, but pelvic examination disclosed no unusual conditions. When seen in the dispensary in June and again on August 4, she seemed well. About the middle of September she had several headaches, and, on one occasion, diplopia. A complete neurologic examination on September 29, however, revealed only normal findings.

During the next few weeks many symptoms developed, and on Oct. 22, 1930, she was admitted to the hospital for the fourth time. The headaches, localized in the left occipital region, had become constant. There were considerable precordial pain and dyspnea, anorexia, vomiting, increasing weakness, and discomfort. The hemoglobin had decreased to 36 per cent, the red cells to 2,240,000. Pelvic examination by Dr. Jones was entirely negative, and neurologic examination by Dr. George W. Hall as late as November 5 revealed no organic changes. An examination of the eyes by Dr. Frank Brawley was negative for evidence of intracranial disease. The urine was normal.

Roentgen films of the chest revealed a mass in the right posterior mediastinum not present at the time of the examination in April, and diagnosed as a metastatic lesion. On October 29, an examination of the skull disclosed a number of regions of increased radiability of the cranial bones, which, in view of the history, were considered compatible with metastatic malignant growths. The sella was within normal limits, and there was no evidence of increased intracranial pressure. Roentgen treatments to the chest were given on November 14 and 15.

During the last few days the patient failed rapidly and numerous metastases occurred in the chest and abdomen. She was discharged from the hospital November 18, because she was unwilling to remain longer away from her children.

Death occurred at home on December 21, 1930. Permission for an autopsy was refused.

CASE 3.—N. McM., a negress aged twenty-nine years, and married for nine years, had two children, four and six years of age. In August, 1930, she had a spontaneous miscarriage of a three months' pregnancy. For a short time after this she had a moderate metrorrhagia. Then followed normal menstrual periods on October 1 and November 5. From December 8 to 31 she had metrorrhagia two to four days and corresponding intervals without. A large blood clot was passed on December 31. When admitted to St. Luke's Hospital on Jan. 3, 1931, her temperature was 101.8° F., pulse 132, and her blood pressure was 88/30. The external os was dilated 2 cm., and from the opening protruded a mass of friable tissue. The corpus was soft and enlarged to the size of a uterus in the third month of pregnancy. The clinical diagnosis was abortion. There was a marked secondary anemia, and a transfusion

was admitted. The left bartholinian gland was palpable, the uterus was enlarged to three times its normal size, and the cervix was widely patulous. After a week in bed she was curetted.

The small amount of tissue recovered included masses of red blood cells, fibrin, traumatized endometrium, and some myometrium. Among the tissue fragments were chorionic villi and masses of syncytium. There was a chronic inflammation of the endometrium.

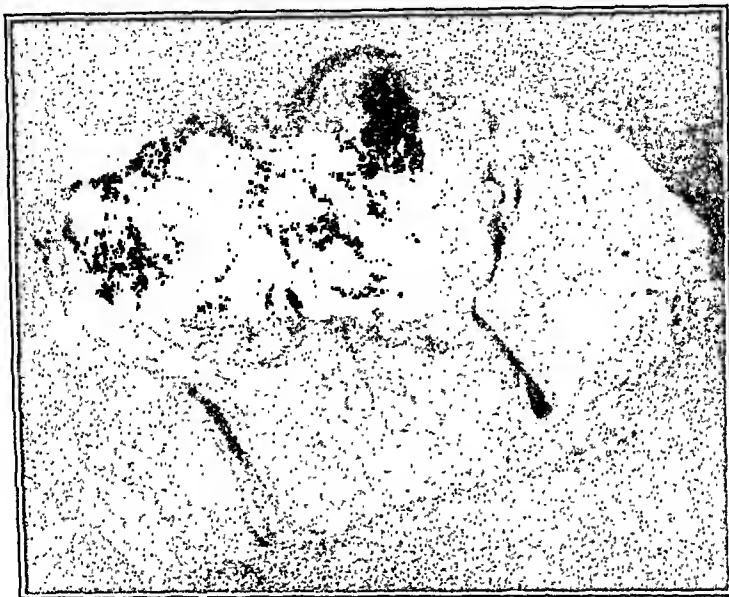


Fig. 2.—Patient 2. The fundic portion of the uterus opened in the mid-sagittal plane. Note the hemorrhagic necrotic nature of the tumor in the vertex.



Fig. 3.—A photomicrograph of the tumor in Fig. 2, illustrating a mass of tumor cells in one of the irregular tissue spaces. $\times 212$

She was discharged from the hospital Nov. 30, 1929, and did not return to the dispensary until Jan. 20, 1930, and then not again until March 10. At both times she was urged to enter the hospital for further treatment of the persistent bleeding. She finally came to the hospital on March 30, 1930. She had no fever, and the pelvic conditions were essentially the same as in the previous November. The uterus was slightly smaller. There was a moderate anemia, the leucocytes were

positive Aschheim-Zondek reaction. The blood pressure had risen to 158 systolic and 98 diastolic. The fundus of the uterus was 17 cm. above the symphysis pubis and 14 cm. wide.

On Jan. 15, 1936, the cervix was dilated and about 1,200 c.c. of hydatid tissue were removed. The histologic examination of this tissue disclosed a hyperplasia of the syncytium and Langhans' cells. The hyperplasia of the syncytium along the margins of the villi suggested the possibility that any tissue remaining in the uterus would continue to grow, and therefore the patient should be kept under close observation for recurrence. There was a moderate secondary anemia; the blood pressure gradually returned to 100 systolic and 70 diastolic. The urine on January 15 produced marked second and third phase Aschheim-Zondek reactions in rats in dilutions up to 1:32, and occasional hemorrhagic follicles above this dilution. The patient left the hospital on January 19.

The Aschheim-Zondek tests each week were strongly positive. The uterus on January 30 was about twice the usual size, and a slight metrorrhagia persisted. After a severe hemorrhage on February 21 the patient returned to the hospital, and

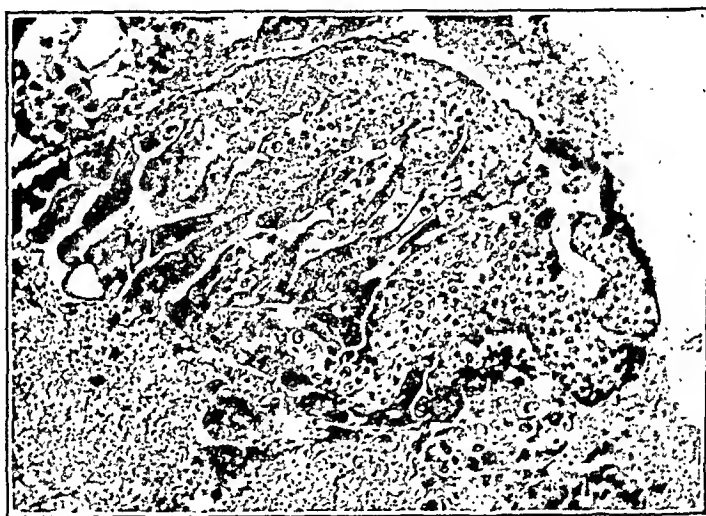


Fig. 5.—Patient 4. Photomicrograph of material obtained at the time of the second curettage. The marked atypical hyperplasia of the chorionic tissues is clearly illustrated. Hysterectomy was urged after viewing this section. $\times 198$

for twelve hours the uterus was packed. Some tissue obtained at this time contained masses of syncytium, trophoblastic cells, large solitary cells with bizarre nuclei, and a few vesicles. In Fig. 5 a typical field is reproduced. On Feb. 28, 1936, forty-four days after the first curettage, the entire uterus and both tubes and ovaries were removed.

The uterus was 11 cm. long and 7 by 5 cm. between the horns. The wall in the anterior mid-sagittal plane was 3 cm. thick. The myometrium was edematous and had many large blood spaces. The lining was granular and hemorrhagic because of the recent curettage. On the left side anteriorly was a mass of soft red brown tissue 3 by 2.5 cm. and 0.5 cm. thick. After the uterus had been hardened in fixing solutions, several segments 2 to 4 mm. thick were cut through and near this mass of red brown tissue. At a level 1.5 cm. below the lining, deep in the muscle of the left side was a hemorrhagic tissue 1.5 cm. in diameter (Fig. 6). Histologic preparations of this nodule contained hemorrhagic necrotic tissue, masses of large solitary cells, and chorionic villi with hyperplasia of the trophoblastic and syncytial cells; a typical microscopic field is shown in Fig. 7.

of 610 c.c. of blood was given. The uterus was curetted and the tissue removed, illustrated in Fig. 4, was reported as chorionepithelioma. Dr. H. O. Jones removed the uterus and both tubes and ovaries on Jan. 14, 1931.

In the lining of the center of the anterior wall, 1.5 cm. above the level of the internal os, there was a slightly elevated mass of tissue with a roughened surface that extended to a depth of 1 cm. In the center of this was a hemorrhagic necrotic region 7 mm. in diameter. Another yellow hemorrhagic nodule at the same level on the right side nearby was 8 mm. in diameter. This was continuous in the wall with the first and extended 1 cm. into the muscle. There were no gross changes of the ovaries or fallopian tubes. The nodules contained much hyalin scar tissue and organizing granulation tissues with scattered large solitary syncytial cells. Several large blood vessels with thick hyalin fibrous walls were present in the scar tissue and in the wall of one of these was a large solitary cell in mitosis.

The Aschheim-Zondek test reported on Jan. 24, 1931, was strongly positive. Two roentgen treatments were given, and the patient was discharged from the hospital on the twenty-first day after her operation. During the next three months six more



Fig. 4.—Curetting from Patient 3, illustrating the irregular masses of chorion, the atypical arrangement of the syncytium and Langhans' layer. $\times 160$

treatments were given. She has remained under observation in the dispensary clinic. The Aschheim-Zondek tests have been negative since she left the hospital. She has no signs or symptoms of metastases.

CASE 4.—H. H., a white woman aged thirty-two years, came under my care on Dec. 6, 1935. Nine years before she had aborted spontaneously in the sixth month of her first pregnancy. Two years later she was delivered at term. Her last menstrual period occurred Oct. 12, 1935, and for a week before consulting me she had had a slight continuous metrorrhagia. The external os was contracted and the uterus was enlarged to the size of an eight weeks' pregnancy. The blood pressure was 114 systolic and 70 diastolic. Metrorrhagia continued for a month although the patient remained in bed. On Jan. 5, 1936, twelve weeks after the last menstrual period, the fundus of the uterus was at the navel and was moderately soft. During the next five days the uterus increased to even greater size and its contour was irregular. Hydatidiform mole was diagnosed clinically. Urine collected during the day and diluted with an equal volume of water produced a strongly

The uterus, both tubes and ovaries were removed on March 6, 1936. The pear-shaped uterus was 14 cm. long, and about 10 cm. wide, and 6 cm. thick between the horns. In the anterior mid-sagittal plane the wall of the body of the uterus was 2.2 cm. thick. The lining surface was rough. Closely adherent in the left cornu was a mass of red brown tissue 7 cm. long, 6 cm. wide, and 3.5 cm. thick. Histologic preparations of this contained masses of red blood cells, fibrin, and necrotic vesicle

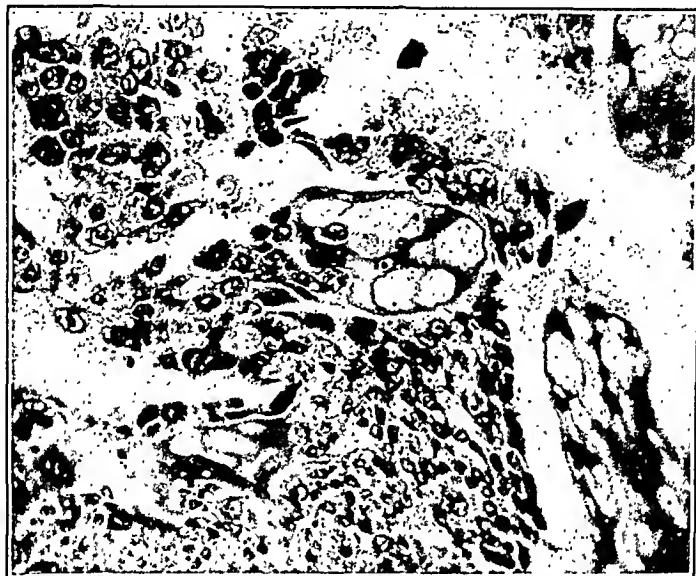


Fig. 8.—Mole tissue curetted from the uterus of Patient 5. Note the marked cellular proliferation and the irregular arrangement of the cells. $\times 212$



Fig. 9.—Photomicrograph of a villus invading a blood vessel in the myometrium. Patient 5. $\times 212$

mole tissue. The deeper tissues included endometrium with many large solitary syncytial cells and adjacent myometrium also invaded by these tissue elements. In Fig. 9, a well-localized metastasis is shown. Masses of unorganized syncytial and trophoblastic cells were found in the necrotic tissues along the caval edge.

The postoperative course was uneventful. The patient left the hospital fourteen days after the operation. The Aschheim-Zondek test on the day of the hysterectomy

Before the operation the patient was given a transfusion of 400 c.c. of citrated blood, and this was repeated one week later. After an uneventful convalescence she was discharged from the hospital sixteen days after the hysterectomy. The Aschheim-Zondek test was negative on the thirteenth day and has remained so since. The patient is well.

CASE 5.—C. K., a white woman aged forty, entered the service of Dr. G. C. Finola at St. Luke's Hospital on Feb. 28, 1936, for the care of her third pregnancy. The other pregnancies had terminated at full term fifteen and nine years before. The last menstruation was Oct. 7, 1935, and during the last part of December she had

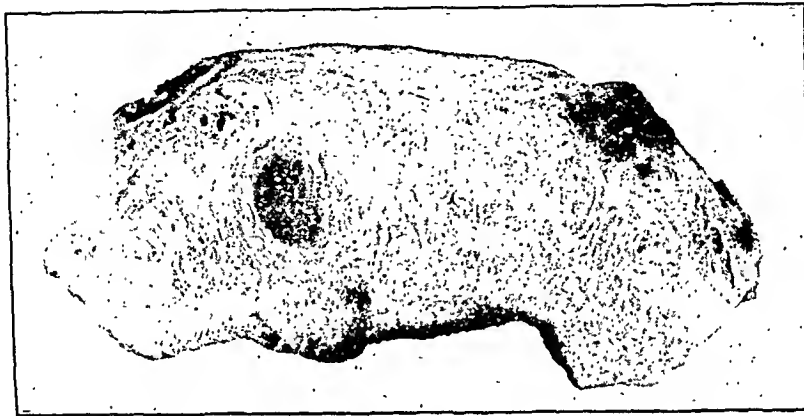


Fig. 6.—Photomicrograph of a metastasis 1.5 cm. in diameter in the myometrium. Patient 4.



Fig. 7.—Photomicrograph illustrating the tissues in the metastasis in the myometrium. Patient 4. $\times 212$

slight metrorrhagia which continued until she entered the hospital. She had not felt any fetal movements, her systolic blood pressure was 184 and the diastolic, 108. The uterus was enlarged to the size of a four months' pregnancy. Therapeutic abortion was indicated because of the patient's age, the high blood pressure, and the metrorrhagia. The uterus was emptied of a large hydatidiform mole on Feb. 28, 1936.

In the histologic preparations there was a marked hyperplasia of the Langhans' and syncytial cells covering the vesicles, and among the cells were many in mitosis (Fig. 8). The Aschheim-Zondek test was positive in a 1:32 dilution of the urine.

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104 SOUTH MICHIGAN AVENUE

DISCUSSION

DR. THOMAS B. SELLERS, NEW ORLEANS, LA.—The records of the private hospital in which I work show an incidence of 6 cases in 4,631 pregnancies during the last ten years. One case followed or complicated hydatid mole. This is a general surgical hospital, about 80 per cent of the work being surgery.

I personally reported one case of chorionepithelioma with hydatid mole in 1923. After removal of the mole the physical condition of the patient was such that hysterectomy would have been a hazardous procedure; therefore radium was used, complete hysterectomy being performed later. A recent report on the condition of the patient shows that she has had no recurrence or complication.

Dr. Gough has already mentioned the difficulty of diagnosing these cases. Inasmuch as an error in diagnosis means a fatal result, more frequent use of the Aschheim-Zondek test is indicated in the presence of histories suspicious of chorionepithelioma.

Emphasis should also be placed upon the importance of complete hysterectomy in these cases.

DR. FRANK W. SMYTHE, MEMPHIS, TENN.—I personally have had experience with chorionepithelioma on only two occasions. Since that time I have had four cases which, while the scrapings were not definite, were extremely suspicious. After hysterectomy in these four cases we found they were placentoma. I would like to ask one question: What value, if any, has the Aschheim-Zondek test in placentoma as compared to chorionepithelioma?

DR. RALPH LUIKART, OMAHA, NEB.—I believe that in a case with a positive Aschheim-Zondek one month postpartum which increases in the strength of the reaction for two months, there is no excuse for further delay in removal of the uterus. All such cases with prolonged positive Aschheim-Zondek tests associated with hydatidiform mole can be saved from chorionepithelioma if properly handled. I would like to have the essayist state why he delayed operation in his case with a prolonged positive Aschheim-Zondek test.

DR. WILLIAM T. BLACK, MEMPHIS, TENN.—It would be interesting to know why under certain circumstances the chorionic epithelial cells continue to proliferate and produce one of the most virulent types of malignancy. Langhans' cells have been found during a normal pregnancy in the lungs, liver, kidney, and other organs, yet these do not usually take on malignant characteristics. There is evidently present during normal pregnancy antibodies or some lytic substance that takes care of these

was strongly positive in a dilution of 1:32; on March 13, one week after the operation, it was entirely negative, as it has remained at monthly intervals since. The patient is in excellent health.

SUMMARY

During the last seven years 5 patients with chorionepithelioma have been observed. In this group the average age was 32.4 years, the youngest was twenty-three, the oldest forty. Three patients were white women and 2 were negroes. In 3 cases the preceding pregnancy was an hydatidiform mole and 2 followed spontaneous abortions. The 2 patients observed before the interruption of the mole pregnancy showed the hypertensive type of toxemia frequently associated with this condition.

The common symptom was metrorrhagia, and this persisted from six weeks to nine months before the cause was determined. Except in the third patient, no definite latent period intervened between the pregnancy and the chorionepithelioma. In the second patient bleeding persisted from the time of the abortion until metastases had developed.

Abdominal hysterectomies were done on all these patients. In 2 only the corpus was excised and in both of these the ovaries were conserved. The last 3 had complete hysterectomies and the adnexa were also removed. Our experience with roentgen therapy has been too limited to justify conclusions.

The one fatality is attributed to the delay in diagnosis so common before the use of the hormone tests. The importance of the latter in the diagnosis of chorionepithelioma is so well established that further comment here seems unnecessary except to emphasize its newness. Such a test was not available when the first patients in this series were observed.

Among the reported cases there have been few diagnostic errors ascribable to these tests, their great usefulness in the detection of malignancy of the chorion has been amply proved. No test, however, can replace clinical judgment, and the value of this agent is dependent on the proper selection of patients; the laboratory report must be interpreted in the light of the clinical history.

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Zondek reaction was due to conservatism. Aschheim in his article in *THE AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY* in 1930 stated that the reaction may remain positive for several months after the expulsion of a mole. Several other authors have concurred in this statement, and have thus obscured the fact that chorionepithelioma may develop in the interim or actually coexist with the mole. One should not complacently accept a positive Aschheim-Zondek reaction as a normal sequel persisting for many weeks after a mole pregnancy.

The importance of the test in the follow-up of any hydatidiform mole cannot be overemphasized. After such a pregnancy, the test should be done at least once a month, in the first month or two, even once a week. Do not be content with one or even several negative results. As an illustration, I refer to the patient reported by Garber and Young in whom a chorionepithelioma developed while a number of Friedman tests were only weakly positive.

TUBERCULOSIS AND PREGNANCY*

G. D. ROYSTON, M.D., JULIUS JENSEN, M.D., AND H. HAUPTMAN, M.D.,
ST. LOUIS, MO.

*(From the Department of Obstetrics and Gynecology, Washington
University Medical School)*

EARLY in this century, it was commonly assumed that pregnancy as a complication of tuberculosis was so serious that it required immediate interference. Sehaute's dictum, that pregnancy in a tuberculous woman called for interruption, gained wide acceptance and is still followed in certain quarters. The drawbacks of childbearing in tuberculous women are obvious. The pregnancy places a strain upon the mother and so does labor. Lactation, besides being a strain on the woman, entails danger of contagion to the infant. Above all, the rearing of children with its added domestic and financial demands is certainly not conducive to the most favorable management of a tuberculous case; it has been justly said that a baby in the home is a greater danger than a baby in the uterus. These are some of the reasons against childbearing in tuberculous women, and they are potent enough to justify the statement that pregnancy should not be undertaken when there is danger that it may be complicated by active tuberculosis. A more lenient view may be undertaken when the tuberculous process is thoroughly arrested. Another problem is: what to do if a tuberculous woman becomes pregnant. This is where an increasing conservatism is gaining ground. Many women with tuberculosis pass through pregnancy and labor apparently unharmed, and when the disease takes an unfavorable turn, it is not possible with certainty to ascribe this turn to the pregnancy. No experiment or clinical evidence shows conclusively that a tuberculous process is affected beneficially or adversely by pregnancy. In recent years, the

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cells. However, as Blair-Bell and others have taught there is under certain circumstances after the death of the fetus and under other conditions, a loss of resistance, and these embryonic cells grow locally and metastasize rapidly to other organs.

A few years ago the speaker reported six cases of chorionepithelioma that occurred in Memphis. While it has been stated by several of the best authorities that chorionepitheliomas follow moles in more than 45 per cent of the cases, it has been shown by Novak, Meyer, and others that chorionepithelioma does not develop after moles in over 1 per cent of cases. In only one case out of the six I have just noted did the chorionepithelioma follow a mole.

Any woman who has a prolonged bleeding after pregnancy should have an Aschheim-Zondek test, and if this is positive, she should have a diagnostic curettage performed. While most of these prove to be placentomas, one will occasionally find the most malignant chorionepithelioma.

DR. ALFRED J. KOBAK, CHICAGO.—The possibility of early diagnosis after expulsion of a mole by the use of the modified Aschheim-Zondek test is a step forward in the early diagnosis of chorionepithelioma. I would, however, like to raise the question of the limitations of the test in the early diagnosis of chorionepithelioma. I had one case where a hydatid mole was expelled and about six weeks after there was a high concentration of hormone in the urine. It proved to be a normal pregnancy. There have been cases in the literature where with the expulsion of a hydatid mole the urine shows no hormonal content and the Aschheim-Zondek test is negative. At the Tumor Clinic of the Michael Reese Hospital I have been shown slides of a syncytioma, in which the preoperative hormonal tests were negative. I would like, therefore, to raise these questions: If we do find a positive test, shown by a high hormonal content of the urine, must we invariably conclude that the patient has chorionepithelioma? On the other hand, if we have a negative test are we safe in concluding that the patient has none? I believe these questions will be answered when more people report their negative findings.

DR. HENRY E. KLEINBERG, DES MOINES, IOWA.—In a recent case of mine of hydatidiform mole expelled at three months, the Friedman test became negative after one month. Since then we have done one more Friedman test and several skin tests with APL, which have all been negative. I feel, however, that this case should be followed for two, three, or four years, because some little piece may be present without giving the hormonal reaction, and it is possible that this area may become malignant later on.

DR. ROLAND S. CRON, MILWAUKEE, WIS.—In a recent case of mine, suspected of having a chorionepithelioma, following an abortion, sections of curettings from a 4 cm. nodule in the right broad ligament showed no evidence of tumor. The hormonal test at that time gave a weakly positive reaction, for only one ovary in each rabbit injected showed any sign of follicle ripening even though undiluted and diluted specimens of urine were subsequently used. This patient developed sepsis following removal of the tissue from the broad ligament with very brisk uncontrollable hemorrhage. Death occurred at the end of about eight days. The lesson to learn from this particular case is that one should use x-ray therapy because it is the only method of saving the patient's life. At autopsy chorionepithelioma nodules were found in the lung.

In another patient operated upon for hydatid mole, chorionepithelioma was found in the uterus. Friedman tests taken before removal of the uterus were entirely negative.

DR. GOUGH (closing).—In the fourth patient, the delay between the first curettage and the hysterectomy in the presence of a persistently positive Aschheim-

among pregnant women on the basis of this material cannot be very accurate. Additional information regarding some of these patients was graciously supplied by St. Louis City Hospital No. 2, Mount St. Rose, and Robert Koch Sanatorium. It was not possible to follow the cases beyond the puerperium; thus the material was seriously impaired.

INCIDENCE

From 1929 to 1934, 10,900 patients were admitted to St. Louis Maternity Hospital and 2,664 were delivered on the out-patient service, a total of 13,570. With 51 tuberculous cases, the incidence was 0.375 per cent. This figure is small considering the estimated incidence of tuberculosis in the general population and the fact that some of these 51 patients were referred from elsewhere because they had tuberculosis and thus would not fairly contribute to a computation of incidence. It is not probable that any considerable number of cases with developed tuberculosis has been overlooked.

DIAGNOSIS

In a pregnant woman, the diagnosis of tuberculosis frequently offers great difficulty. The more important signs were found only in a certain number of the cases. Tubercle bacilli were found in the sputum in 13 cases, hemoptysis in 19, but in 12 of these it was slight and in only one was it very severe. Cough was present in 24 but in 18 it was listed as being slight; in only 2 was it severe. Thirteen gave a past history of pleurisy. Up to the time of delivery, fever was not common. In only 15 cases was it noted and in none of these was it very marked. Persistent râles and other marked physical changes were found in 22 cases; in 22 the findings were doubtful. Excepting cases of advanced tuberculosis, interpretation of x-ray films caused much difficulty. Many persons who are not clinically suffering from tuberculosis present on x-ray examination findings suggestive of this infection. Thus, x-ray findings must be interpreted with as much care as most other single pieces of evidence. In the present series, cavitation was seen in 3 cases, in 34 the x-ray findings were strongly suggestive, in 13 they were indeterminate. In only one case did the examination fail to show changes. Thus, while it is possible that some patients have been included in this series who did not have tuberculosis, these are probably very few, partly because of the strict criteria and also because the total number of cases was proportionately so small.

CLINICAL COURSE

On the whole, the clinical course was favorable. Only 2 patients died, 3 became definitely worse, 2 showed some aggravation of the disease: a total of 7 of the 51 patients became worse during pregnancy.

profession has manifested a growing interest in this subject, and closer study has resulted in increasing reluctance to interfere with the pregnancy. Follow-up studies have failed to show that the later fate of tuberculous women (excepting, perhaps, those having the serious caseous-pneumonic type of lesion) was affected by childbirth (Barnes and Barnes, Garshell, Ornstein and Kovnet). Also, if children of tuberculous mothers are carried to term, they are usually born healthy. There is little evidence that premature emptying of the uterus benefits a tuberculous woman, especially when the pregnancy becomes advanced. Some tuberculosis is likely to progress in spite of any measures that may be undertaken. The result has been an upward trend toward a more conservative attitude on the part of the medical profession, especially if the tuberculous process appeared to be arrested. The present study is a small contribution attempting to test the justification of such a stand.

MATERIAL

Fifty-one cases of pulmonary tuberculosis seen at the St. Louis Maternity Hospital during the years 1929 to 1933 were tabulated and analyzed. An additional seven patients probably also had tuberculosis, but the diagnosis could not be established beyond a reasonable doubt. Unless the disease is advanced or tubercle bacilli are found in the sputum, the diagnosis of pulmonary tuberculosis must remain largely a matter of judgment. These records were largely evaluated according to the criteria established by the Trudeau Sanatorium.* Some cases were accepted on the basis of previous opinions of some of the leading tuberculosis specialists in St. Louis. Thus, probably every advanced and moderately advanced case is included, though some latent and early cases may not have been discovered during the routine physical examination. The patients were admitted to the St. Louis Maternity Hospital either through their private physicians or through the Washington University clinics. Some, again, were referred to the University clinic from the St. Louis Municipal prenatal clinics which possess no special obstetric medical clinic. Thus, this material was drawn from an ill-defined field, from which it is impossible to obtain the total number of admitted patients, and where the thoroughness with which the patients were examined for tuberculosis must have varied. Thus, an estimate of the incidence of tuberculosis

*The criteria for the diagnosis of tuberculosis at Trudeau Sanatorium are:

1. History or presence of pleurisy with effusion.
 2. History of hemoptysis (1 dr. or more).
 3. Presence of moderately coarse râles above the third rib and the third vertebral spine.
 4. Parenchymatous change demonstrable by x-ray above the third rib and the third vertebral spine.
 5. Presence of tubercle bacilli in the sputum.
- One or more of these findings is necessary for a positive diagnosis.
All must be absent to exclude tuberculosis.

section and sterilized because of the tuberculosis. Only two labors were prematurely induced, one at three and one at four months. Both were private cases. This illustrates the conservative stand of the profession. Of the 9 cases which ended spontaneously before term, two patients miscarried at two months, one at three months, one at six months, four at seven months and one patient died when five months pregnant. Considering that many of these patients had fever, the results cannot be considered unfavorable.

TABLE III. COURSE OF PREGNANCY IN TUBERCULOSIS

		Spontaneous	9
Premature deliveries-----	12	Induced	2
		Cesarean	1
Normal deliveries at term-----	39		
Average weight of 31 babies-----	3316	grams	

ETIOLOGIC FACTORS

Tuberculosis was twice as common among ward patients as among private patients. There were 4,113 private patients and 9,457 ward patients or a ratio of 1 to 2.3. Among the private cases, 9 had tuberculosis against 42 ward patients, or a ratio of 1 to 4.7. A history of contact cannot easily be gathered from old records. Of these 51 cases, there was no mention of contact or family incidence in 36 but in 12 there was tuberculosis in parent, sister, brother, or child, and in 3 more there was tuberculosis in grandparent, uncle, or cousin.

Tuberculosis prevails in the colored race. Among the 6,111 admissions to the St. Louis Maternity Hospital for 1932 to 1935 inclusive, there were 1,348 colored patients or a ratio of 1 to 4.5. Among the 51 patients with tuberculosis, 19 were colored, a ratio of 1 to 2.7.

TABLE IV. INCIDENCE OF COLORED PATIENTS AMONG TUBERCULOUS PATIENTS.
ST. LOUIS MATERNITY HOSPITAL 1932-35

TOTAL CASES		TUBERCULOUS CASES	
Colored	1348	Colored	19
Total	6111 = 22.1%	Total	51 = 37.3%

TABLE V. AGE INCIDENCE AMONG TUBERCULOUS PREGNANT WOMEN

1. Control (Lundh and Wachenfeldt)		
24 years or less	5910	= 29.6%
Total	19621	
2. Tuberculosis (our series)		
24 years or less	19	= 37.3%
Total	51	

Norris and Landis found that the incidence of tuberculosis is especially high among women aged fifteen to twenty-five years. They associated this finding with the occurrence of first pregnancies at this time. Among the total of 19,621 cases analyzed by Lundh and Wachenfeldt, there were 5,910 aged twenty-four years or less, 29.6 per cent. Among the present 51 patients, 19 were aged twenty-four years

Theoretically, pregnancy may have three possible effects on the tuberculous process:

1. It may increase the immune powers of the patient; this view is supported by the facts that pregnancy increases the immunity against certain other infections and that many tuberculous women feel particularly well during pregnancy.

TABLE I. COURSE OF TUBERCULOSIS IN PREGNANCY

Declined	2
Definitely worse	3
Died	2
	—
Worse	7
Not affected	44

2. The strain of pregnancy may be too much for the tuberculous patient and result in a breakdown of her resistance. In favor of this view are the observed cases of aggravation of the tuberculosis during pregnancy, but this has not been proved to occur more frequently than would be expected among nonpregnant women. The duration of symptoms among the present group offers another point in support of this second view. While no information was available in 16 cases and 5 patients had no symptoms, 20 of the remaining 30 patients gave a history of having had symptoms six months or less. Most of these patients were seen in the second half of pregnancy, which makes it appear that in 40 per cent of the entire series and in 66 per cent of those in which the duration of symptoms was noted it is probable that these appeared after the onset of pregnancy. While neither the number nor the nature of the present material permits conclusions on this point, it at least suggests that pregnancy may be an activating factor in cases of latent tuberculosis. Of the other 10 cases, 3 had had symptoms between seven and twelve months, 1 between one and two years and 6 over two years. On the other hand, there is no evidence to show that pregnancy increases the usual liability of tuberculosis to become more severe.

3. Pregnancy might in no way affect the tuberculous process and the observed changes might be coincidental. So far, the accumulated evidence is insufficient to decide this question.

TABLE II. DURATION OF SYMPTOMS

DURATION	NO SYMPTOMS	0-6 MONTHS	7-12 MONTHS	1-2 YEARS	2+ YEARS	NO INFORMATION
Cases	5	20	3	1	6	16

In many cases, the symptoms had developed recently, possibly after the onset of pregnancy.

THE EFFECT OF TUBERCULOSIS ON PREGNANCY

One case was seen only during pregnancy and could not be traced. Thirty-eight patients went to term and spontaneous labor. In 8 of these, the weight of the child was not stated; the average weight in the remaining 31 patients was 3,340 gm., which would indicate that the tuberculous process had had no effect on the infants of these patients. One of these children was stillborn; it weighed 4,000 gm. and the mother had, in addition, toxemia. Of the 12 patients who did not have spontaneous labor at term, one was delivered at term by cesarean

1. Is the mother living or dead?
2. Has she sought any medical attention since that delivery? If so, what for and where?
3. Has she had any symptoms such as: (a) cough, (b) fever, (c) loss of weight, (d) night sweats, since the delivery in question?
4. Has the mother been pregnant again since the delivery in question? What was the termination of each delivery? What is the *condition* of the children resulting from these pregnancies?
5. What is the *condition* of the children resulting from the pregnancy in question?

TABLE VII. FOLLOW-UP SERIES

1. Mothers	Living Dead	33 1	Total Traced 34	NUMBER OF PATIENTS	
				YES	NO
2. Subsequent Medical Attention				29	5
Periodic chest examination				11	
Pneumothorax Clinic				4	
Obstetric Clinic				8	
Tuberculosis Clinic				3	
Gynecology Clinic				3	
Mental Asylum				1	
Unclassified				3	
3. Incidence of Symptoms					
Subsequent to Delivery:					
Cough		5			
Fever		2			
Loss of weight		4		5	29
Night sweats		1			
4. Fate of Children					
Normal		24			
Stillborn		4			
Abortion		2			
Delicate		3			
Died at 8 mo.		1			
5. Subsequent Pregnancies:					
Normal infants		6		8	26
Abortions		2			

CONCLUSIONS

This series of 51 cases is too small to permit of definite conclusions. It has been compiled to contribute toward such an accumulation of data as may permit of conclusions being drawn. While it is possible that pregnancy may activate a resting lesion, there is no other evidence that the course of the disease is adversely affected thereby, nor is there any evidence that tuberculosis, except in its febrile stages, adversely affects pregnancy if the case is properly handled. The chief difficulty in compiling such a series lies in the evaluation of diagnostic findings. If the criteria are too strict, many cases will be missed; if they are not strict enough, too many tuberculous cases will be admitted.

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or less, 37.2 per cent. From these figures it would appear that the incidence of tuberculosis is high in young women. Among Wachenfeldt's 26,481 cases, 11,378 were primigravidas, 42.9 per cent. Among the present 51 cases, 18 or 35.3 per cent were primigravidas. Thus, this material does not support Norris and Landis' assumption.

TABLE VI. PARITY AMONG TUBERCULOUS PREGNANT WOMEN

1. Control (Wachenfeldt)		
Primigravidas	11,378	= 42.9%
Total	26,481	
2. Tuberculosis (our series)		
Primigravidas	18	= 35.3%
Total	51	

COMPLICATIONS

The complications which occurred were mostly tuberculous in nature or caused by tuberculosis: Secondary anemia (4), tuberculous laryngitis (2), Pott's disease (1), tuberculous cervical adenopathy (1), and tuberculous meningitis (1). Some were obstetric in nature: Toxemia (2), pernicious vomiting of pregnancy (1), and positive blood culture postpartum (1). Finally, two developed psychosis and one pyelonephritis. Five had positive tests for syphilis, a finding which is not surprising considering the large number of colored patients in the series.

TREATMENT

The principle of conservatism is to be stressed. As long as tuberculosis is inactive, the patient should be treated expectantly with the best medical and hygienic measures. At the first sign of activity, sanatorium treatment or its equivalent is imperative. In this connection, it is interesting that one sanatorium near Dresden, Germany, has a separate division for tuberculous pregnant women. A few years ago, Alice Hill surveyed the sanatorium facilities for pregnant tuberculous women in this country. She found them entirely inadequate, in fact they were worse for pregnant women than for tuberculous women who were not pregnant. It appears that the situation has since undergone some improvement. The time when obstetric interference is indicated in active tuberculosis must always remain a matter of individual judgment; the life of the child must be considered as seriously as the life of the mother. Most cases can probably be carried to term and then delivered, if necessary, by cesarean section and then sterilized. When patients go downhill rapidly, it must be determined to what extent this may happen independent of the pregnancy. In hopeless cases, the life of the mother should be prolonged, if possible, in the interests of the child.

The follow-up of our patients included the results from the following questionnaire, personally conducted by the Social Service Department of the St. Louis Maternity Hospital.

THE TREATMENT OF CERVICOVAGINITIS IN CHILDREN WITH SILVER PICRATE SUPPOSITORIES*

A PRELIMINARY REPORT

ALFRED J. KOBAK, M.S., M.D., AND LESTER E. FRANKENTHAL, JR., M.D.,
F.A.C.S., CHICAGO, ILL.

(From the Mandel Clinic of the Michael Reese Hospital)

THE treatment of cervicovaginitis as recorded in the literature of the past decade has been subjected to frequent changes. A lack of uniformity of treatment is evidenced, in the literature of any short period, by the variety of therapy advocated. The following methods of treatment have been used (some with good and others with indifferent results): Mercurochrome, silver nitrate, aeriflavine, vaccines, diathermy, copper ionization, antiseptic irrigations, and lately the popular usage of estrogenic hormones. The frequent variation of therapy by the investigators treating this clinical entity is an indication that no one has found consistent success with any single form of treatment.

Cervicovaginitis may be divided into two distinct types: (1) Specific or gonorrheal, which in general is the more severe and more difficult to cure; and (2) the nonspecific, which has been found to have less severe symptoms and is caused by a variety of organisms, and is frequently more amenable to therapy. Both forms of vaginitis are characterized by a vaginal discharge, which may vary in its intensity. Examination shows localized evidences of inflammation by the presence of a discharge ranging from slight to profuse in amount and from serous to mucopurulent in consistency with a tendency to crust when it dries on the skin. The vestibule and vulva have an irritated appearance. The vagina and cervix are likewise affected in varying degrees of intensity. Beyond these local findings, one rarely observes any systemic or generalized complications. Many of these children are undernourished and may have some degree of secondary anemia. This ailment is found most frequently in the poorer classes where hygiene is bad.

The management of these patients has two objects. First, and most frequently stressed, is the local treatment to eradicate the causative organisms; and second, the improvement of local hygiene by cleanliness, and the general health by a well-balanced diet with addition of vitamin therapy whenever possible.

*Read at the Eighth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Detroit, Mich., October 15-17, 1936.

Kovnat, Maurice: Am. Rev. Tuberc. 31: 224, 1935. (5) *Schwarz, Otto H.:* Fetal, Newborn and Maternal Morbidity, White House Conference on Child Health and Protection, New York and London, D. Appleton-Century Company, p. 67.

DISCUSSION

DR. JOHN ALEXANDER, ANN ARBOR, MICH.—A crucial point in the discussion of this interesting subject is, in my opinion, whether the pregnant patient has active or inactive tuberculosis. Inactive tuberculosis is frequently diagnosed as "tuberculosis" and, quite obviously, persons with old, inactive tuberculosis may proceed to term with reasonable safety. In the category of active tuberculosis there is almost every degree of activity. Patients with mildly active fibroid tuberculosis run relatively little risk from pregnancy, provided the tuberculosis is expertly managed both during pregnancy and after delivery. On the other hand, patients with the unstable, partially exudative type of tuberculous lesion are exposed to a very considerable risk of serious progression of their tuberculosis if their pregnancy is allowed to proceed to term. We have recently had at the University Hospital, among 100 tuberculous patients, two who died of tuberculosis following delivery, and another whose tuberculosis became activated following delivery, although her disease had been brought to a quiescent state by collapse therapy shortly before she became pregnant. When faced with the problem of a patient who has become pregnant in the presence of active tuberculosis, I feel we should ask ourselves the question, If this woman were not pregnant would we permit her to become so at this time? If the answer is in the negative, and if the pregnancy is less than four months old, I believe the patient should be aborted and the tuberculosis actively treated in a sanatorium. After the tuberculosis has been arrested for two, three, or more years (depending upon the case), consideration should be given to permitting the patient to become pregnant with the reasonable expectation that she could then bear a healthy child without risk to her own health and life, and that she might care for the child without exposing it to a great risk of tuberculosis infection and death. Royston and Jensen's data show that only 3 of their 51 patients had cavitation, only 13 had tubercle bacilli in the sputum, and 19 had hemoptysis; it is likely that most of the patients with cavitation and tubercle bacilli are included among the 19 who had hemoptysis. From the data presented I doubt if more than half of the 51 patients, namely 26 patients, had active tuberculosis. If this is true, then 7 out of a possible 26 patients with active tuberculosis became worse or died of tuberculosis during or after pregnancy which, I submit, expresses a very considerable risk. In conclusion, I believe that patients found to have active tuberculosis during the early period of pregnancy should be seriously considered for therapeutic abortion.

DR. G. D. ROYSTON, ST. LOUIS, MO. (closing).—The outcome in a given case depends almost solely upon the period of the infection. Barnes and Barnes found that the pneumococcus type of lesion was present in over 60 per cent of their cases. In the case that has liquefaction and cavity formation, the mortality is higher. The report of Barnes and Barnes, Garshell, Ornstein and Kovnat has shown that pregnancy has little effect upon tuberculosis, although the favorable cases improve at the onset of pregnancy, and the active cases get worse even though the uterus is not emptied. We must add that adverse domestic and financial factors react unfavorably upon tuberculosis. The demands of the children in the house keep the mother from getting proper rest.

We must remember that if the pregnancy is to be interrupted, better results are obtained if this is done early. In former years I was a very active advocate of the teaching that therapeutic abortion should be done for tuberculosis. Today I have reversed myself because if tuberculosis is treated as tuberculosis, the patient may be permitted to go to term.

findings, and the smears were all negative for three successive months. However, the children were observed for longer periods whenever possible.

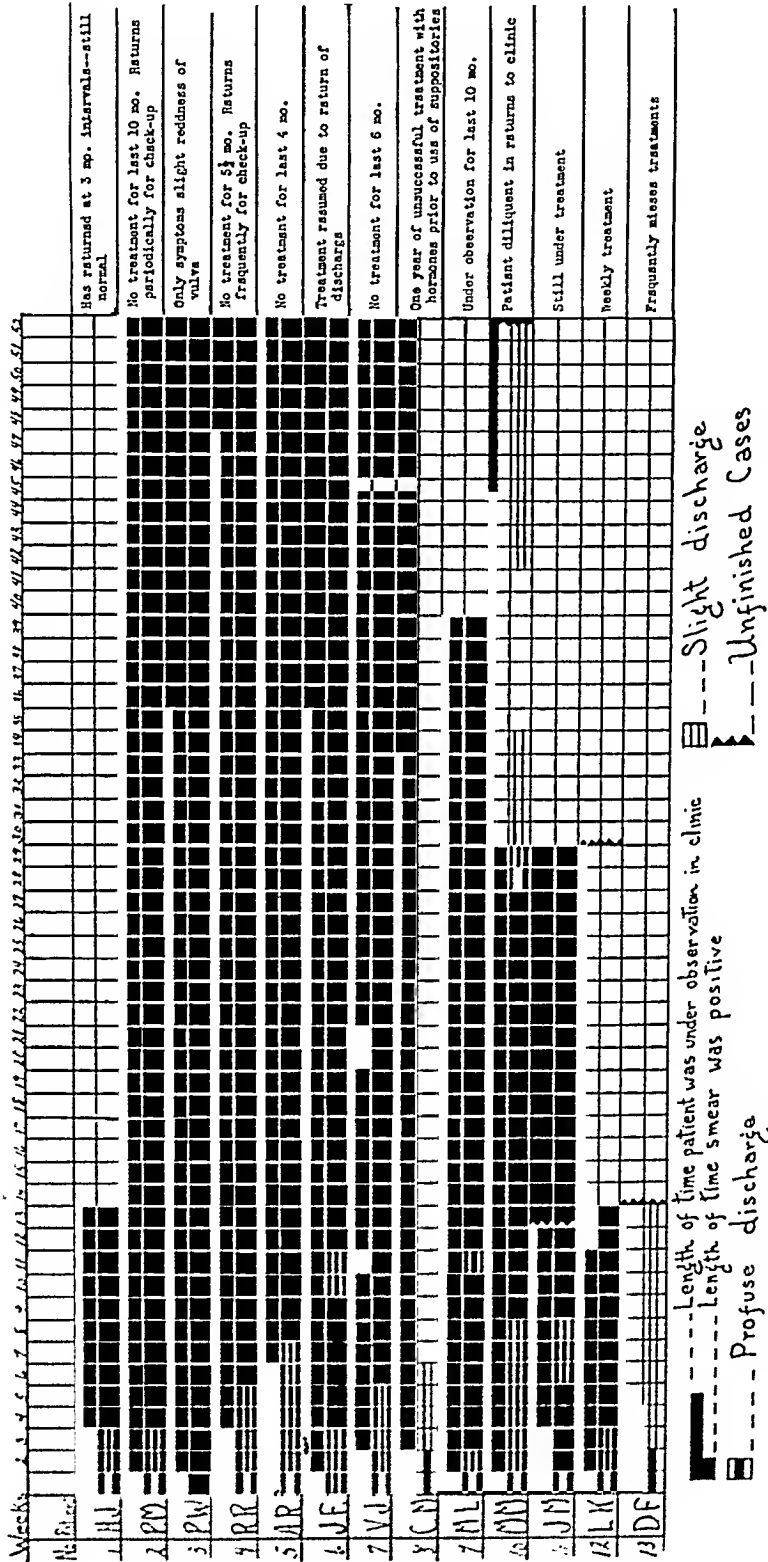


Fig. 1.—Results in the treatment of patients that had smears positive for the gonococcus.

The results of this form of treatment, as shown in Figs. 1 and 2, are self-explanatory. The patients showed rapid and definite improvement as evidenced by the quick disappearance of the discharge. The recorded observations of the mothers also

The vaginitis clinic of the Michael Reese Hospital was established by Irving Stein, who personally supervised it up to seven years ago. The treatment advocated by him and his associates¹ consisted of daily injections of 1 per cent mereurochrome 220, incorporated in hydrous wool fat mixed with an equal amount of petrolatum. The mixture was first warmed to render it soft, and then injected at room temperature, high into the vagina. The mothers were instructed how to do this, and when necessary, nurses made visits to supervise and personally treat the child. Stein found results of this treatment to be very satisfactory. These procedures were continued by us for four years but it was felt, despite the good results obtained, that there was room for some improvement. Primarily, we noticed that the ointment rapidly oozed out and stained the garments of the child, which mothers reported to be objectionable. The efficacy of this treatment was therefore felt to be impaired by the rapid loss of much of the material injected. An attempt was made to study other methods of therapy and possibly find one that would insure easier application. A form of medication was desired that the mothers could easily apply by themselves, and one that would find its way into all the crypts of the vaginal canal and still not be expelled prematurely with subsequent loss in its efficiency. The latter was our experience with all ointments. A silver picrate suppository was adopted because it answered these objections and has been tried for one year. Our results with its usage are the basis of this preliminary report.

METHOD OF TREATMENT

The patients were examined at each visit with the infant vaginoscope, and thereby, the condition of the cervix and vagina was observed and progress notes made. By means of this instrument, a smear was taken from the vaginal portion of the cervix. When insufficient material was obtained from this source, smears were also taken from the vagina. The mother of the patient was instructed to cleanse the vulva between the labial folds daily or more often with a soft cloth, and to use bland soaps such as castile or super-fatted types. The insertion of the suppository was demonstrated to the mother at the child's first visit. She was instructed to keep the suppository in the refrigerator to maintain its maximum rigidity and for lubrication to use only cold water. During the hot weather, an instrument was devised to facilitate in the introduction of the suppositories. A supply of suppositories was furnished with further instructions to inject every night before bedtime so that the chance of its premature expulsion would be minimized. This treatment was to be omitted the night before the next visit to the clinic. The mothers were likewise instructed as to diet whenever the child appeared undernourished. Many of our patients are under the care of the department of pediatrics.

At each visit a record was taken of the mother's statement as to the progress made and she was asked whether there was any discharge from the standpoint of the child's clothes being soiled by contact with the genitals. Daily treatment was administered by the mother until the discharge and signs of inflammation disappeared, and the smears became negative. Then the treatment was gradually spread out until the patient was receiving no local treatment and merely returned for purposes of smear examinations. The patient was considered cured when the discharge, local

duction (intramuscular), unless there is a beneficial effect of the basic content of the suppository which in TeLinde's series was glycerin and carbolic acid.

The more rational treatment is one that aims at the immediate etiologic agent by direct application of an antiseptic substance on the diseased tissue, and the indirect treatment by improvement of the local hygiene and general health of the child. Schaufler very aptly stated, "The time-worn theory that the infantile canal is carpeted by a thin, weakly resistant mucous membrane is untenable, as proved by repeated gross and microscopic examinations. In the infant and small child, the vaginal canal constitutes an ideal 'harbor of infection,' whereas in the adult it does not. Obvious characteristics of the immature vagina account for the mechanical retention of organisms and for changes in the secretions favorable to their existence. These are (1) hymenal occlusion (relative); and (2) the contracted cryptiform accordion-like conformation." The illustrations of this contributor well support his contentions. The suppository adopted and used in our series was of such size that it should readily pass the hymen, and of such length that it occupied the entire length of the vagina. It has a boroglycerin gelatin base. The dosage of silver pierate was 1 gr. to each suppository. It melted readily at body temperature and appeared to diffuse easily throughout the surface of the vagina into its crypts. The material was observed to adhere well to the vaginal surface with which it came in contact. The series of cases that make up this report, is not very large. Four additional patients in whom we were obtaining good results, did not return to complete the treatment. In view of the encouraging results obtained in this small series in so short a period of time, we will continue to study this treatment.

SUMMARY AND CONCLUSIONS

Twenty-two patients with cervicovaginitis were treated with silver pierate. Thirteen were found to have positive smears for gonococcus. The results obtained were considered very encouraging.

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DISCUSSION

DR. HARRY M. NELSON, DETROIT, MICH.—Cervicovaginitis in children is primarily a public health or clinic problem. The average gynecologist sees none or perhaps very few cases, and the pediatrician does not treat many. Therefore, we must depend for most of our knowledge of this condition on our public health clinics.

In 1935 the Social Hygiene Division of the Detroit Board of Health treated 97 cases of gonorrheal vaginitis in children, by instillations of 10 per cent protargol solution in glycerin, given weekly. The mother was instructed to irrigate the

confirmed this improvement. Five of the patients had a permanent negative smear after one week of treatment, and three became negative in three weeks. Four patients became permanently negative after six to nine visits to the clinic. Only one patient remained resistant to treatment and did not become permanently negative until fifteen clinic visits had been made. The nonspecific group likewise showed a rapid response to this therapy.

DISCUSSION

The treatment with silver picrate as outlined was easy for the mothers' use. The group of patients treated in our series consisted of seven negroes and fifteen whites. We felt that the cooperation of the class of mothers we were dealing with could be assured only when their duties

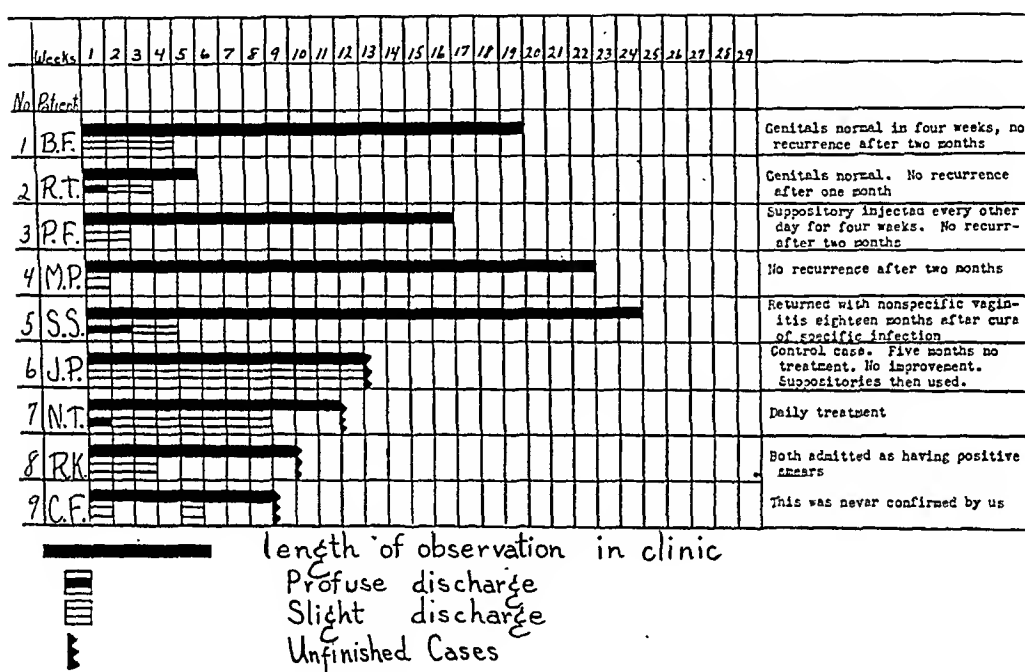


Fig. 2.—Results in treatment of nonspecific vaginitis.

were easy to comprehend and did not entail too much effort. Before starting to use the silver picrate suppository, we had also tried neisogel injections, and estrogenic hormone. Both methods of therapy proved unsuccessful in our hands. The hormone injections, besides being expensive and painful to the child, have not given the satisfactory results claimed by others. Witherspoon² and Sehauffler³ were not encouraged by their results with hormone therapy. TeLinde and Brawner⁴ observed very good results following the use of estrogenic hormone in the vaginal suppository form. Here the rationale of this treatment was ease of administration. The effect was indirect, i.e., after the systemic absorption the action of the hormone is referred back to the vaginal mucosa to bring about its beneficial changes. It is hard to conceive that local benefits of hormone can be better achieved this way than by direct systemic intro-

if findings continue to remain negative, we eventually have the patient returning to our clinic, although she has had no suppository injections at all. Thus many of our patients are seen at two- and three-month intervals merely for observation.

Our standard of cure is three consecutive monthly smears that are negative, together with absence of all other findings. We try to have our patients come as long as possible to check against any possible recurrence.

Our results with estrogenic hormone have been disappointing. We have had six patients under this form of treatment and gave them as much as 2,000 units a day. After long periods of time our patients were still uncured by accepted standards. One patient had a positive smear after eleven months of treatment with associated profuse discharge and local findings of acute vaginitis. When we transferred this patient to the present form of treatment the smear became permanently negative in one week and the discharge disappeared shortly thereafter. We followed this patient for ten months and never noted any recurrence.

After one year's usage of this suppository treatment we have felt very much encouraged by the good results that practically always followed. We have had no anal infections. We had one case of bartholinitis before we tried this form of treatment. We had none of the adult complications, but we did find cervical lesions. There were small erosions and the portio vaginalis often appeared injected. To make these observations we depended upon the vaginoscope. Without its use we could never see what changes were occurring above the hymen, and thus have a direct check on the progress the patient was making during the course of treatments.

MATERNAL MORBIDITY*

SIX YEARS STUDY OF 4,837 CASES AT THE EVANSTON HOSPITAL

ROBERT M. GRIER, M.D., EVANSTON, ILL.

(From the Department of Gynecology and Obstetrics of Northwestern University Medical School and of the Evanston Hospital)

IN THIS report is presented a study of morbidity occurring in the cases delivered in the Maternity of the Evanston Hospital beginning in 1930 and continuing through 1935. In these six years 4,837 women were delivered of 4,885 viable babies. There were 5 deaths, a mortality rate of 0.10 per cent. There was only one death from puerperal infection. The American College of Surgeons standard for morbidity has been used. Any woman whose temperature rises to 100.4° F. on any two or more days, not including the day of delivery, has been considered morbid. Temperatures have not been taken every four hours. A morning and evening reading only is taken as a routine. If fever appears, the temperature is taken every four hours until normal. According to Stander bidaily temperature readings instead of four-hour readings reduce the incidence of morbidity to one-third.

Including cesarean sections the gross figure of morbidity was 6.5 per cent. When these are excluded the incidence was 5.0 per cent. It will be seen therefore that this operative procedure increased the incidence by about 30 per cent.

*Read at the Eighth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Detroit, Mich., October 15-17, 1936.

child at home twice daily, with a weak solution of potassium permanganate. This was done over a period of four weeks when smears were taken. If five successive smears were negative the patient was said to be cured. The average length of treatment for all ages was 103.5 days, for those under five years, 132 days, and for school children 89 days.

The sources of infection may be of interest. There was a positive source discovered in 60, or 66.6 per cent. In 54 per cent sources were found in the home; in 6.6 per cent the origin was a sexual contact; 5.5 per cent were said to be contracted cases; 4.4 per cent of the cases were contracted in hospital nurseries.

Our method of hormone therapy has been to give 100 rat units of theelin each day for a week, then three times a week until negative smears are obtained. In the majority of cases we obtain negative smears in four to six weeks. This treatment seems to cut down the duration of the disease though we do not know what effect it may have on the child in the future or what effect it may have on the ovaries.

DR. IRVING F. STEIN, CHICAGO.—Some years ago I found at Michael Reese Hospital that some cases of vaginitis in children came to the pediatricians, a few to the gynecologists, a few to urologists, and no one group agreed on a uniform plan of treatment. We suggested that the three departments come together, but after we had organized a special clinic, pediatrics and urology dropped out of the picture and left the problem to me entirely. Since then I have been able to maintain interest in the subject in the Gynecological Department.

In the literature there is great enthusiasm expressed in favor of hormone treatment, but my own experience with it was discouraging. I want to commend the routine use of the vaginoscope in examination. I have never seen any harm come from its use, and have never had to stretch or cut the hymen in order to insert the instrument. I get a great deal of helpful information from its use in cervicovaginitis.

DR. H. C. HESSELTINE, CHICAGO.—The use of the vaginoscope has been justly stressed. I would like to emphasize again its value in diagnosing the occasional case of a foreign body. The diet, particularly with regard to the vitamins, is most important.

Have any of these patients had reactions? This question is raised as I have been reliably informed that an occasional adult may have such a reaction. If this reaction is the result of ionization with formation of peric acid, then perhaps there is less likelihood of such in the child because of the comparatively low acidity, even alkalinity of the vaginal moisture.

Were there any cervical infections, and if so, what other therapy than suppositories did you use? How many of the gonorrheal patients had anal infections, and how were these infections treated?

DR. KOBAK (closing).—The change in the content of the smears is one way of observing the progress the patient is making. In the beginning we find the smears to be full of leucocytes and these contain morphologic forms of gonococci. As the patient improves there will be a disappearance of the gonococci but the pus cells predominate. With continued improvement epithelial cells are seen in increasing numbers, and as they do so the pus cells become progressively diminished in numbers. In the cured case we see nothing but the epithelial cells and occasional bacteria.

When we first began to use the silver picrate suppository we were uncertain when to advise the mothers to discontinue the injection of the suppository. Our experience soon taught us to advise the treatment daily until all signs of inflammation had vanished, the discharge reported absent by the mother, and the smears negative. Then we instruct the mothers to increase the intervals between the injections and,

are included. It will be seen, however, that the morbidity of this procedure differs but little from that of spontaneous delivery, namely from 3.8 per cent to 5.2 per cent.

Parity alone appeared to influence morbidity very little. In the 4,837 women in this report 48 per cent were primiparas and 52 per cent were multiparas. In the 319 morbid patients this proportion was about the same, 46 per cent were primiparas and 54 per cent were multiparas.

Other obstetric maneuvers and accidents are found to contribute to morbidity. We have studied some of these, such as cervical tears, induction of labor, spontaneous or artificial rupture of the bag of waters and uterine packing. Table II shows that the risk of morbidity is definitely increased when a cervical tear is produced. Perhaps the slight increase for breech extraction is due to the smallness of this series. In the entire series, however, the increase is 120 per cent.

TABLE II. MORBIDITY AND CERVICAL TEARS, 1930-1935

TYPE OF DELIVERY	NUMBER DELIV- ERIES	NUMBER TEARS	% TEARS	% MOR- BID GEN- ERAL	NUM- BER MORBID WITH TEARS	% MORBID WITH TEARS	% INCREASE MOR- BIDITY OVER GENERAL
Spontaneous	2,267	109	4.8	3.8	7	6.4	60
Breech extraction	158	17	10.7	7.6	1	8.3	9
Low forceps	1,994	158	7.9	5.2	22	12.7	154
Midforceps	165	38	23.0	13.3	9	23.6	77
Podalic version	80	9	11.2	16.2	3	33.3	105
Total	4,664	331	7.9	5.0	42	12.4	120

Induction of labor was studied only for the past four years during which time accurate figures have been kept. The usual procedure for the induction of labor is a modified Watson method. Some men have employed a warm soapsuds enema instead of the castor oil. As a rule we do not attempt induction of labor unless there is some effacement and dilatation of the cervix. The colpeurynter was used sparingly, nine times, and then only for placenta previa or severe toxemia in multiparas. There were 292 inductions in 2,045 deliveries or 9.5 per cent. Twenty of these were morbid, an incidence of 6.8 per cent which is practically the figure for the entire group. In our experience medical induction does not increase morbidity.

Among the patients who were morbid there was almost an equal number with membranes ruptured spontaneously or artificially and this corresponds with the experience in all the deliveries. The average time from rupture of the membranes to delivery in the cases in which spontaneous rupture occurred was 11.4 hours. In the cases in which the membranes were ruptured artificially, it was 2.3 hours. In this

The ratio of morbidity according to the type of delivery has been analyzed and is shown in Table I.

TABLE I. RATIO OF MORBIDITY, 1930-1935

TYPE OF DELIVERY	BABIES DELIVERED	% INCIDENCE OF METHOD	% MORBID	RATIO
Spontaneous	2,267	46.4	3.8	1
Low forceps	1,994	40.7	5.0	1- 1.3
Breech extractions	158	3.4	7.6	1- 2.0
Midforceps	165	3.2	13.3	1- 3.5
Podalic versions	80	1.6	16.2	1- 4.2
Cesarean section	221	4.5	38.5	1-10.1
Total	4,885	99.8+	6.5	1- 1.7

If the incidence of morbidity for the spontaneous deliveries is taken as a basic figure, 3.8 per cent, and if we call this one, we can forecast the increased risk of morbidity for the other types of delivery. A chart indicating the increase of morbidity for the various obstetric operations has been posted in our delivery rooms as a warning to us all. Next to cesarean section, midforceps and version and extractions carry the highest incidence, 13.3 per cent and 16.2 per cent, respectively. The frequency as compared with spontaneous deliveries is 3.5 to 1 and 4.2 to 1. Thus it is shown that the more radical the procedure the greater the risk of morbidity.

Version and extraction was done in only 1.6 per cent of our cases. Midforceps deliveries were done in 3.2 per cent, the incidence being less than that of cesarean section, which was 4.5 per cent. We hope to reduce the frequency of abdominal delivery, as its morbidity rate is 38.5 per cent or ten times that of spontaneous delivery. In a former report the author showed the high incidence of fetal mortality for version and extraction. This same group of operators promptly reduced the incidence by about one-half to its present low level. When one realizes the dangers of a procedure it is usually avoided far more than would be thought possible.

Other factors influence morbidity beyond question. Some of these will be shown. It is generally agreed that puerperal infection may arise from foci of infection elsewhere in the body. This can be controlled partially by the elimination of such foci early in pregnancy. We all strive to do this with our private patients as well as with clinic patients. Infection was shown by Semmelweis and Holmes to be carried to patients by the physician through the lack of asepsis. Eradicating this faulty technic was a great step forward. Now perhaps we are too complacent with our "good" aseptic technic. I think that our record is not good and not bad, but can be improved. By reducing our operative procedures to a minimum, especially those that show a high rate of morbidity, we believe we can reduce our figure considerably. Our incidence of operative deliveries is high if outlet forceps

cent and multiparas 53 per cent. Induction of labor is not too widely used but withal sufficiently often, 9.5 per cent. The method used has been described.

The vaginal and perineal preparation solutions used have been green soap and mercurochrome, acetone, and alcohol. Since November of 1935 for economical reasons, we have been preparing a compound colored alcoholic solution of mercuric chloride for skin disinfection. This was described by Vaichulis and Arnold from the Department of Bacteriology and Public Health of the University of Illinois. It can be prepared for \$1.60 per gallon. So far we have not noticed an increase in infections, and are satisfied with its use.

The personnel of the delivery rooms has been the same as far as nursing supervisors are concerned for far longer than the six years included in this report. There is a training school for nurses in the Evanston Hospital and each pupil nurse receives six weeks of obstetric training in the delivery rooms.

There were three internes on the obstetric service for three months at a time, each constantly on duty in the maternity for a shift of at least eight hours a day. They assisted with all deliveries. For the past three years, most of the time, we have had a clinical clerk, a fourth-year student from Northwestern University Medical School, who assisted with all deliveries. They remained with us on twenty-four-hour duty for six weeks.

TABLE V. PERSONNEL

DISTRIBUTION OF DELIVERIES	NUMBER DELIVERIES	PER CENT OF DELIVERIES
Staff	2,992	62.0
Internes (clinic)	618	12.8
Courtesy obstetricians	621	12.8
General practitioners	606	12.4
Total	4,837	100.0

To Dr. William C. Danforth, who has been the Chief of the Department of Obstetrics and Gynecology for the past fifteen years, goes much of the credit or responsibility for this record. He has established its technique and policies. He has trained, to a great extent, all of the three other members of the staff. The work distribution is, I think, unique for a general hospital (Table V). Most of the women, 62 per cent, were delivered by the staff. In addition 12.8 per cent were clinic patients who were delivered mostly by the internes, but always under the direct personal supervision of one of the staff. Another 12.8 per cent were delivered by six nonstaff obstetricians who are trained men and limit their practices to obstetrics and gynecology. Only 12.5 per cent were delivered by 44 different men in general practice. Practically all of the latter men confine their obstetrics to the simpler procedures and call consultation freely when complications are feared.

series then we can say that very little effect was noticed in the morbidity rate for spontaneous or artificial rupture of the membranes.

Uterine packing was employed quite freely when indicated. We believe that anemia or loss of blood increases the risk of infection very materially, and such has been the common experience of most obstetricians. Thus, we do not wait until a great deal of blood is lost before packing the uterus with from 5 to 10 yards of gauze, but resort to this procedure whenever the uterus tends not to stay contracted. It was used in 2.1 per cent of our cases (Table III). It is more widely

TABLE III. MORBIDITY FOR UTERINE PACKING, 1932-1935

TYPE OF DELIVERY	NUMBER PACKED	% PACKED	% PACKED MORBID	% MORBID GENERAL	% INCREASE MORBIDITY OVER GENERAL
Spontaneous	17	1.3	5.8	3.8	52
Low forceps	24	1.6	29.1	5.0	480
Breech extraction	7	6.2	0	7.6	0
Midforceps	8	10.3	0	13.3	0
Podalic version	7	14.0	28.5	16.2	75
Total	63	2.1	15.8	5.0	216

used after the difficult operative maneuvers or prolonged labor. The morbidity rate was thus naturally high, 15.8 per cent, for all uterine packings. It is hard to say what the rate would have been had the patient been allowed to bleed more extensively.

The technic in the delivery rooms has been essentially the same with but few exceptions. The use of rectal examinations has been employed as a routine. However, vaginal examinations are done occasionally if deemed necessary. Most of the time during the past few years 4 per cent mercurochrome has been injected into the vagina prior to a vaginal examination and the doctor always puts on a sterile gown and gloves. The patient has a complete perineal preparation. In the last three years sodium pentobarbital and scopolamine have been used in 62 per cent of our cases during labor. This has been mentioned as a factor likely to increase morbidity. Except for the first year of its use when there was a sharp increase, our morbidity has been getting less than before. Table IV shows these yearly comparisons.

TABLE IV

	BEFORE USE OF NEMBUTAL			AFTER USE OF NEMBUTAL		
	1930	1931	1932	1933	1934	1935
Per cent morbid	7.7	6.9	6.5	8.3	5.7	4.4
Per cent three-year averages	7.0			6.1		

Artificial rupture of the bag of waters has been done in approximately half of the cases. In the morbid cases this was practically the same ratio. Frequent use is made of episiotomy, in primiparas 86 per

3. Uterine packing carries a high rate of morbidity but should not be delayed too long as the hemorrhage is equally dangerous.

4. Maintenance of good delivery room technique is very important. This can best be maintained by an unchanging nursing staff.

5. Excellent obstetrics may be done in a general hospital where the majority of the work is done by a well-controlled group of trained obstetricians.

6. An analysis of work, for which good records are essential, tabulated monthly and yearly is all-important in preventing laxity and is a stimulus to better work.

DISCUSSION

DR. WINTON T. STACY, ST. JOSEPH, MO.—Any statistical study that is done of work in a hospital tends to improve that work. This report of 5 to 7 per cent gross morbidity is about the average morbidity one will get in looking over well-regulated institutions. If you get a rise in morbidity, look to your work. This report emphasizes (1) conservative obstetrics, (2) the necessity of an organized, well-trained obstetric nursing staff, (3) the supervision of courtesy obstetricians and general practitioners, and (4) a standard of morbidity.

The standard of morbidity used here made no mention of a rise of temperature after the tenth day postpartum nor inclusion of fatal cases. Bidaily readings were recorded. Some of us believe that if readings are made every four hours we would get an increased morbidity. It is interesting to note that 19 per cent of the patients had fever on admission. Temperature is a symptom. Many men have advanced the theory that we should base our morbidity records not only on temperature rise, but upon any evidence of definite or prolonged pathologic condition with or without fever, resulting from childbirth, because definite pathology has been found in patients whose temperatures never reached 100.4° F. Almost every childbirth leaves a little damage, therefore accepting this standard of morbidity we would get a direct proportion to parity. Using rise of temperature as an index for morbidity this is not true, as shown by the essayists. Perhaps we use temperature readings because two or more can read a thermometer alike, whereas it is often difficult for two, equally competent men, to agree upon a diagnosis of a pelvic inflammatory condition.

The relation of the seasons of the year to morbidity was not discussed. Some increase in morbidity, due to upper respiratory tract infections, may be expected during the winter months. I do believe we have more unaccountable temperature elevations during the hot summer months. During the past summer in a study of morbidity I attributed it to the external temperature, 110 to 112° F.

Morbidity may be the first step toward mortality. Dr. Grier has brought out the fact very clearly that morbidity is directly proportional to the severity of the operative procedure, and has worked out a ratio chart that would be well to have in every obstetric ward. In this respect his findings are similar to those of other writers, but do not agree with those who find a direct proportion between (1) length of labor, (2) rupture of membranes, (3) vaginal or rectal examinations and morbidity.

This paper, through and through, is an argument for conservative obstetrics with minimal interference, and then only when indicated. It is proof of the fact that excellent obstetrics may be done in a general hospital where properly trained men supervise the work of those doing obstetrics, calling attention to their results by means of tabulation of the work done.

This being one of the requisites of the courtesy privileges extended to them. This control of the work and the continuance of the same trained personnel and essentially the same birth room technic, which was familiar to all, was one of the principal reasons for these results. A careful detailed tabulation of all work is kept day by day so that from month to month and year to year results are known and can be studied. Any man who does not do continually good work is removed from working privileges or reprimanded. Any procedure showing unsatisfactory results was done as little as possible or eliminated.

An analysis of the different diagnoses given for the 319 morbid patients was made. It is not essentially different from those in other reports, but is given here as a matter of record. Sixty of these women, or 18.8 per cent, had some fever on admission. Puerperal infection, including metritis, endometritis, parametritis, peritonitis, pelvic cellulitis, phlebitis, and puerperal infections, accounted for 75.2 per cent of the morbid (Table VI). Mastitis was the cause of fever in 8.7 per cent of our cases, being next to the puerperal group in frequency.

TABLE VI. CAUSES OF MORBIDITY

TYPE OF DELIVERY	NO. MORBID FOR TYPE	PUER- PERAL IN- FECTION		MASTITIS		PYELITIS		RESPIRA- TORY		EXTRA- NEOUS	
		NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
Spontaneous	87	58	66.1	11	12.6	6	6.9	5	5.7	8	9.1
Low forceps	100	75	75.0	13	13.0	2	2.0	10	10.0	1	1.0
Breech extraction	12	6	50.0	2	16.6	-	-	2	16.6	2	16.6
Podalic version	13	10	76.1	1	7.7	-	-	1	7.7	1	7.7
Midforceps	22	17	77.2	1	4.5	3	13.5	1	4.5	-	-
Cesarean section	85	74	85.8	-	-	2	2.3	5	7.5	4	4.6
Total	319	240	75.2	28	8.7	13	4.0	24	7.5	16	4.9

Respiratory infections accounted for 7.5 per cent. These included ordinary colds, laryngitis, bronchitis, bronchopneumonia, lobar pneumonia, and pulmonary tuberculosis. In 4.0 per cent of the febrile cases pyelitis was found. All the others, or the fevers from extraneous causes, amounted to 4.9 per cent. In this latter group are included two cases of acute endocarditis both of whom died, with positive blood cultures of hemolytic *Streptococcus viridans*.

In conclusion, this study, we think, has shown us that morbidity can be reduced.

1. Reduction to a minimum of the more radical types of delivery such as, midforceps, high forceps, version and extraction, and cesarean section is most essential.

2. The number of cervical tears should be reduced as much as possible by conservative obstetrics and the avoidance of the more extensive forms of intervention.

LYMPHANGIOMA OF THE OVARY*

R. S. SIDDALL, M.D., AND W. R. CLINTON, M.D., DETROIT, MICH.

(From the Department of Obstetrics and Gynecology and the Department of Surgery, Harper Hospital)

TRUE lymphangioma seems to be among the rarest of the tumors arising in ovarian tissue. In fact, until 1908 the existence of such a growth was doubted. In that year Kroemer reported two authentic cases. In a search through the literature we have found the report of one other tumor which was probably of this type, although the author (Fleischer) believed it to be lymphoeystic degeneration of the ovary. Rössle reported a lymphangioma found in the ovary of a ten-month-old child, which, however, had developed from subcutaneous tissue in a dermoid cyst. Sehottländer's third case was probably also of this kind, and therefore not a tumor originating in true ovarian tissue. The tumor reported below we believe to be a true lymphangioma developing within and from the ovary.

CASE REPORT

Negress (Harper Hospital Case No. 122106), forty years old, married for a number of years but never pregnant. She complained of a mass in the abdomen which had been present for two years and had enlarged considerably during that time. There had been progressively developing dull pain which was most marked at time of menstruation. Constipation had been present since the onset of her trouble, and for six months before admission there had been slight swelling of the ankles. The patient also complained of a femoral hernia. The past history was unessential except for the fact that the menstrual periods had been irregular and frequent with intervals of only six days to three weeks. They had also been profuse at times. At the last period, ending one week before admission to the hospital, there had been bleeding for eight or ten days with cessation for one and one-half days and then bleeding again for six days.

Physical examination showed nothing noteworthy except marked obesity, blood pressure of 180 systolic and 100 diastolic, slight edema of the ankles, and a lower abdominal tumor. This tumor could be felt as a firm nodular mass extending up to the level of the umbilicus in the midline and somewhat to the right. It was movable above but was fixed in the pelvis at its lower pole. On the day after admission, operation was performed under novocaine spinal anesthesia. Supravaginal hysteromyomectomy, bilateral salpingo-ovariectomy, appendectomy, and bilateral femoral herniorrhaphy from within the peritoneal cavity were done. The postoperative course was febrile from the second to the sixth day with the highest temperature 102° F., but was otherwise uneventful.

The specimen consisted of the uterus (amputated supracervically), fallopian tubes, ovaries, and the appendix. The uterus measured 18 by 13 by 10.5 cm. due to many fibromyomas of which one at the fundus was the size of an orange and another

*Read at the Eighth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Detroit, Mich., October 15 to 17, 1936.

We should adopt a standard of morbidity. As yet, we must accept an elevation of temperature to 100.4° F. on two consecutive days not including the day of delivery nor after the tenth postpartum day. The method of taking temperature is of little importance.

DR. IRVING F. STEIN, CHICAGO.—I would like to emphasize what Dr. Grier brought out and what Dr. Stacy seconded, that the amount of kind of interference is a most important factor in producing morbidity. I would like to emphasize one other point, namely, that antiseptics play a very minor rôle in prophylaxis. At Michael Reese Hospital a number of years we have used various external antiseptics, starting with bichloride external douche over the perineum, in the preparation, and the use of bichloride solutions for frequent rinsing of the gloves, during delivery. Then we used lysol, and later we painted the perineum with one-half strength iodine. Then mercurochrome was tried. Even antedating the Mayes' technique, we used external but not internal mercurochrome antiseptics in obstetric preparation. Then after a few years we decided that sterile water was just as good if our technique was improved. We compared a given number of cases prepared with sterile water taken at random from our records with an equal number in which the agent of preparation was mercurochrome, iodine, and later merthiolate, using Mayes' technic for the latter, and we found the morbidity in each series about the same percentage. We do not feel that antiseptics play any important rôle. In consequence we have eliminated even the hand basins containing antiseptics that we used for rinsing gloves and use sterile water instead, and our morbidity has shown no increase over the years in which we did use the various antiseptic agents.

I would like to bring out one other point, that after two serious accidents with bichloride solution in the hospital in our department, we have persuaded the general staff and the administration of the hospital to eliminate bichloride of mercury from the hospital. At the present time with a wide selection of antiseptics which are adequate for thermometer sterilization, and other instrument sterilization that formerly called for bichloride, we believe that bichloride should be eliminated from hospital routine and available only if ordered specifically from the drug room by a given physician. I think that is a distinct step forward in teaching asepsis, and in eliminating these unfortunate accidents which occasionally were encountered.

DR. GRIER (closing).—Of the five deaths we had in this series the causes of death and the types of delivery were as follows: (1) Puerperal infection following spontaneous delivery. (2) Acute endocarditis following spontaneous delivery. (3) Acute endocarditis following cesarean section. (4) Postpartum hemorrhage following cesarean section. (5) Lobar pneumonia; patient was delivered at home and brought to the hospital immediately following delivery.

We do not believe that antiseptics play a great part in morbidity, consequently we are using the solution mentioned which can be made as cheaply as possible, namely \$1.60 a gallon. We think that morbidity can be reduced and the following conditions are of great assistance: (1) A well-controlled staff of trained men. (2) Proper delivery room supervision and careful maintenance of technique, and, (3), avoiding the more radical types of delivery. I think the figures in this report indicate this. We are also convinced that a study of this kind has helped us. In checking up on our results we will find when to reduce this morbidity. In a previous report, we have found that our fetal mortality following version and extraction was entirely too high, consequently delivery by this method has been reduced 50 per cent.

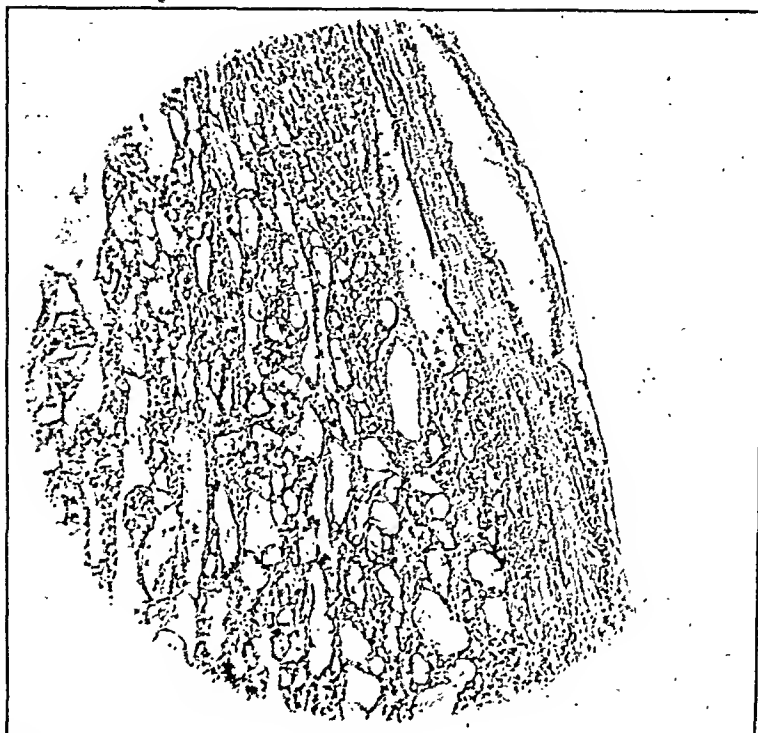


Fig. 1.—Lymphangioma of the ovary. Low power showing the lymph spaces and also the connective tissue capsule of the tumor.



Fig. 2.—Lymphangioma of the ovary. High power showing the endothelial-lined lymph spaces.

smaller one just above the point of amputation measured 4 by 4 by 3 cm. Both tubes appeared normal, and the right ovary showed nothing of note except several small cysts. The left ovary was of special interest. It was pear-shaped, measuring 8 by 7 by 5 cm., and was somewhat uneven in contour but not definitely nodular. The consistency suggested a solid tumor, but there was not the degree of firmness as is found with such tumors as fibromas. Cut section showed a uniform, light colored, and well-defined solid tumor occupying all of the mass except for a crescent-shaped and compressed layer of ovarian tissue fitting like a cap over one end. This ovarian tissue contained several small cysts.

Microscopic examination, except for the findings in the left ovary, was of little interest. The largest fibroid showed areas of hyaline degeneration, and rather sparsely glandular endometrium was in an early proliferative phase. Cysts of the right ovary were of the simple follicle type. Both tubes and the appendix were normal.

Sections from different parts of the tumor in the left ovary showed essentially the same picture throughout, the structure consisting largely of spaces lined by a single layer of endothelium and varying in size from that of small capillaries up to eight to ten times their diameter. A few spaces contained coagulated material in which were occasional small or large round cells. The spaces were obviously lymph vessels. The endothelium showed no buds or other evidence of proliferative activity. In some parts of the tumor the lymph vessels lay directly against each other, but usually there was a layer of connective tissue between. This stroma or framework was usually very thin, and nowhere was it broader than the width of the medium-sized lymph spaces. It was composed of connective tissue of a loose fibrillar and sparsely cellular type with the cell nuclei rather large and round, or spindle-shaped. There were no areas of extensive or advanced degeneration in the tumor, though the endothelium of a few vessels showed pyknotic or faintly staining nuclei. Also, the stroma in numerous, but scattered and small, areas between the lymph spaces had undergone hyaline degeneration with disappearance of nuclei. These changes were more common in the deeper portions of the tumor. Nowhere was there obliteration of the lymph vessels, mass necrosis, or cyst formation.

The tumor was surrounded for most of its circumference by a thin capsule of fibrillar connective tissue resembling that found between the lymph vessels and in which there were similar though larger areas of hyaline degeneration. The fibrils lay parallel to the surface of the tumor, and from them the connective tissue framework of the tumor proper seemed to originate. Over a small part of the periphery the capsule thinned away and finally seemed to disappear so that the lymph vessel development was covered by the germinal epithelium only. In the capsule there were a moderate number of rather large lymph vessels and also a few small blood vessels and capillaries. In the tumor proper was seen only one small area with blood vessels. This was just beneath the capsule, and there were only a few, scattered, blood-filled capillaries lying among the lymph spaces. Elsewhere in the tumor all the spaces were obviously lymph vessels. There was a small round cell or lymphocytic infiltration throughout the connective tissue framework and capsule. In the latter were seen several small collections of lymphoid cells resembling tiny lymph nodules.

At one pole of the tumor was the thin crescent of ovarian tissue with the points extending about one-third around the periphery. Here was found normal appearing ovarian tissue, mainly the cortical type. There were several developing follicles and two structures resembling small follicular cysts, in one of which was fresh (traumatic?) blood. The tumor was stripped away from the normal appearing ovarian tissue for the most part, but where still attached its capsule showed a transition or merging of tissue and cell type into that of the denser and more cellular ovarian cortex.

was also a lymph vessel tumor, but here was a structure suggesting sarcoma. Both the endothelium and the stroma cells were undergoing active proliferation and had become round cell in type. The endothelial lining of the larger lymph spaces was reduplicated to form a many-celled layer. He suggested the possible progression of a lymphangioma to such a picture or even to that of malignant endothelioma.

We wish to thank Dr. Plinn F. Morse for his kind assistance and permission to use this material from the laboratory.

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DELIVERY FOLLOWING STILLBIRTH FROM DYSTOCIA IN PREVIOUS PREGNANCIES*

ARTHUR B. HUNT, M.D., AND ROBERT D. MUSSEY, M.D.,
ROCHESTER, MINN.

(From the Section on Obstetrics and Gynecology, the Mayo Clinic)

THE obstetric patient who becomes pregnant after having lost her first baby from dystocia presents a problem of more than ordinary interest. Her case represents a challenge to the attending physician to obtain a live and healthy baby with a minimum of risk to the mother. Often the history of the first delivery, which resulted in death of the fetus, may be incomplete or vague, and the physician must supplement such information with careful objective findings during pregnancy and at term to decide on the best method of conducting labor. In spite of this, however, plans for delivery frequently must be revised, without much notice, at term or after the patient is in labor.

Because a review of the literature (of the last twenty years) has failed to reveal a specific reference to cases of this interesting group, we feel our rather small series of cases merits report. We wish to present a series of 33 consecutive patients who in the last ten years came to the Section of Obstetrics at the Mayo Clinic with the history of having lost their first baby in labor or shortly thereafter as a direct result of some form of dystocia. There were 38 stillbirths among these 33 patients, as 5 patients had each had 2 stillbirths before coming to the clinic. None of these 33 patients was therefore the mother of a live baby. Dystocia is here interpreted in its broad sense as any difficult labor or delivery,

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Pathologic Diagnosis.—(1) Cavernous lymphangioma of the ovary. (2) Fibromyomas of the uterus, hyaline degeneration. (3) Follicle cysts of the ovary. (4) Normal fallopian tubes and appendix.

COMMENT

Histologically, our tumor agrees very closely in every respect with those described by Kroemer, except in one particular. His tumors were both large (the largest being twice the size of a child's head) and doubtless because of their size had undergone advanced necrosis and cystic degeneration in their central parts. This was apparently similar to the frequent finding in the deeper portions of large lymphangiomas from other parts of the body. Fleischer's tumor was somewhat smaller than ours, measuring 7 by 5.5 by 5 cm. The endothelial-lined spaces varied in size from that of a pinhead to a lentil. There was no evidence of degeneration except for a loss of endothelium in some of the spaces. He preferred the diagnosis of lymphoecystic degeneration rather than lymphangioma, chiefly because there were no suggestions of active endothelial proliferation such as are found in lymphangiomas of the lip, tongue, and cheek. Evidences of rapid endothelial growth were likewise lacking in our tumor, but the picture was definitely that of an enlarging though circumscribed and benign neoplasm. Kroemer evidently considered his tumors to be newgrowths and was careful to differentiate them from lymphangiectasis. He even questioned their essential benignity as will be mentioned later.

The infrequency of lymphangiomas of the ovary is established so far as published reports are concerned. However, Kroemer doubted their extreme rarity and expressed the belief that many had been overlooked because of the lack of a distinctive gross appearance. Yet, in the twenty-eight years since his report it would seem that a number of these tumors, if they are not actually highly infrequent, would have been found by chance and been reported. Meigs states that he has never seen one in the pathologic material from the Massachusetts General Hospital, and our case is the first to be found during the last five years at Harper Hospital among approximately two thousand microscopically examined ovaries.

Because of its apparent infrequency, lymphangioma of the ovary is at present of little importance clinically. For the same reason, its prognosis in respect to recurrence has not been determined though pathologically our tumor appears to be benign and examination of the patient twenty-two months after operation showed no return of the growth. Unfortunately, our patient did not return for observation after discharge from the hospital. Kroemer was unable to follow his patients, and Fleischer gave no subsequent history for his case. Kroemer considered his tumors to be potentially malignant because of a third growth found in an ovary next to an atretic follicle. This

According to the histories, the incidence of immediate maternal morbidity was not great. Three patients, however, had a history of having been febrile and confined to bed for a month or more. Later morbidity was evidenced in 8 cases by the extensive vaginal and perineal scars. There was one third-degree laceration and one rectovaginal fistula.

An inquiry into the incidence and type of pelvic contraction is pertinent. Seventeen of the 33 patients in the series had definite pelvic contraction, general contraction in 7 cases, funnel in 4, flat in 3, and in the remaining 3 unspecified. Four additional patients apparently had normal pelvises, but there must have been a serious dystocia as evidenced by the history and subsequently by failure of the test of labor. In 1 case dystocia was due to a definitely oversized fetus. In 4 cases the live baby which was delivered subsequently through the pelvis was of greater weight than the stillborn fetus of the first pregnancy; 3 of these subsequent deliveries were spontaneous, 1 was a midforceps delivery.

One may conclude, we believe, that in these cases either soft tissue dystocia or premature operative interference was the cause of stillbirth at the first delivery. As further evidence of this, 10 of these patients were later delivered of their infants through the pelvis with relative ease.

DELIVERIES AFTER PREVIOUS STILLBIRTH

The method of delivery to be employed for parous women whose babies have previously been born dead makes an interesting study. As term approaches a selection must be made of those patients for whom a test of labor may be tried. The fact that a woman has lost a baby from dystocia does not indicate, per se, that elective cesarean section must be employed routinely in subsequent deliveries.

The following analysis of deliveries subsequent to labor resulting in stillbirth will show that often no single criterion will decide which cases are suitable for the test of labor. Disproportion is the most important single factor. Twelve patients in the series were not allowed a test of labor but were submitted to elective cesarean section. Nine of these 12 had contracted pelvises, and in most instances the head could not be depressed to the ischial spines. The average weight of the fetus was 8 pounds (3.6 kg.). In the 3 remaining cases without pelvic contraction, placenta previa was present in 1, a second patient had already had 2 previous stillbirths, and in the third case the head of a very large baby was unengaged as labor began.

The remaining 21 patients in the series were allowed a test of labor. Seventeen of them were delivered through the pelvis, with 1 fetal death. In the 4 remaining cases, in which the test of labor failed, the patients were delivered by cesarean section. There was, therefore, only 1 stillbirth in this group of cases, and this delivery was classed in the group in which the test of labor failed because the baby was lost. The test of

not only from actual bony disproportion between the fetal head and maternal pelvis, but also from other causes, such as malfunction of the pelvic soft parts or anomalies in presentation of the fetus.

In all but a few cases the fetus was at or near full term and was of sufficient weight and maturity to withstand at least the rigors of an average labor and delivery. In the few cases in which the fetus was not so sturdy because of prematurity, actual cephalopelvic disproportion existed.

ANALYSIS OF PREVIOUS DELIVERIES

Nine of the 33 patients had been delivered as primiparas at the clinic; the remainder had been delivered elsewhere. The 5 patients who had had stillbirths twice had likewise been delivered elsewhere. The average length of labor for 18 of these 33 women had been thirty-two hours and twenty minutes, although a third of these primiparas had labored sixteen hours or less. The average age at the time of previous delivery was twenty-six years and two months, or about the average for primiparous women seen at the clinic. Four of the patients in the series were less than twenty years of age, 5 more than thirty, at the time of the previous delivery. The oldest was thirty-seven years old; therefore, the elderly primigravida was not frequently seen in this series.

An analysis as to the cause of the first stillbirth in some of the cases cannot be entirely accurate, owing in some instances to the difficulty of obtaining an accurate history of what transpired at the first delivery; in most cases, however, the cause of previous stillbirth could be rather readily determined.

Operative delivery with its frequently accompanying trauma had been necessary in 22 cases. Bony disproportion was estimated in these cases to have been present in 16 instances. Dystocia resulting from the dysfunction in the pelvic soft parts had been encountered in at least 5 instances and probably more. Breech presentation had been recorded in 6 instances, about 6 times the normal incidence, which is usually given as approximately 3+ per cent. There was one face presentation.

While no searching inquiry as to the employment of pituitary extract in labor was made, its injudicious use in 2 cases probably explained the fetal deaths. The history was especially clear in 1 case. There was also 1 instance of prolapsed cord associated with a contracted pelvis.

The data as to the method of the previous delivery were not available in 4 cases. In 12 cases delivery was referred to as "instrumental," usually implying forceps delivery. Six patients had been delivered by breech extraction, in 3 cases forceps having been applied to the after-coming head. A clear history of 3 midforceps and 2 high-forceps deliveries was given, and 2 craniotomies had been performed after a high-forceps operation had failed. One fetus was stillborn by cesarean section after a high-forceps delivery had failed.

TABLE I. FETAL MORTALITY

	LIVING	DEAD	PER CENT MORTALITY
First delivery (at clinic or elsewhere)	0	33	100.0
Second delivery (elsewhere)	0	5	100.0
Second delivery (in five cases the third)	32	1	3.1
Third and subsequent deliveries	16	1	9.3
Total deliveries after first stillbirth	48	2	4.0
Corrected fetal mortality*			2.0

*On basis of 1 fetal death in 50 deliveries subsequent to stillbirth, the other infant dying of a congenital anomaly and urinary infection eighteen days after cesarean section.

In viewing the results, then, of 50 deliveries subsequent to stillbirth from dystocia, there were 2 (4 per cent) fetal deaths, 1 from stillbirth and 1 neonatal death on the eighth day from a congenital anomaly. Deducting this latter death as having no connection with delivery, the corrected fetal mortality is 2 per cent. Since all infants were stillborn in the first delivery, the fetal mortality can be said to have been reduced 98 per cent for the series. In the 88 deliveries, there was 1 maternal death from sepsis on the third postpartum day following elective cesarean section, making a maternal mortality of about 1 per cent. Because of the high incidence of conditions conducive to dystocia (for example, more than half of the patients had contracted pelves), a somewhat higher maternal mortality might have been expected.

In 10 cases there was puerperal morbidity (a temperature of 100.4°F. on two successive days on any day from the second to the ninth, inclusive); all 10 patients were delivered by cesarean section.

SUMMARY AND COMMENT

Thirty-three patients, all of whom had lost one or more babies in a previous pregnancy from difficult labor and delivery, were delivered at the clinic. In 50 such subsequent deliveries, there were only 2 fetal deaths, 1 a stillbirth and the other from a congenital anomaly, or a corrected mortality of 2 per cent. There was only 1 maternal death from sepsis (1.0 per cent). The maternal morbidity was 20 per cent, and this occurred only in cases in which cesarean section was performed. Following delivery through the pelvis, there was no maternal mortality or febrile morbidity and only one baby was lost.

Three factors producing the dystocia that was present at the first delivery are not usually seen at the time of the second delivery: (1) soft-tissue dystocia, (2) breech and other abnormal presentations, and (3) the injudicious use of pituitrin in the first stage of labor. In certain instances these conditions seemed to explain the stillbirth at the first pregnancy. A test of labor may well be advised in such cases provided there seems to be no cephalopelvic disproportion. The test of labor was successful in 76.2 per cent of the cases in which it was employed. In

labor was accordingly successful in 16 of the 21 cases or 76.2 per cent. There was no maternal mortality in this group.

The most complete report of the results of trial of labor to come to our attention is that of Bailey and Williamson. They reviewed 676 cases in which patients in labor had contracted pelves and observed that 90.1 per cent delivered through the pelvis with a maternal mortality of 0.44 per cent and a gross fetal mortality of 6.2 per cent. We feel that our results of the test of labor compare favorably with this experience when one considers that all of our patients had previously had stillborn infants from dystocia.

As has been said, 5 patients had previously had 2 stillbirths each. One of these patients with a normal pelvis was successful in subsequent test of labor and delivered from below spontaneously; all of the others were treated by cesarean section, one after an unsuccessful test of labor. The pelves of 2 of these 4 were normal, of the other 2, contracted.

In 3 of the 6 cases of original breech presentation, there was a recurrence of breech presentation. One patient was delivered successfully (breech presentation), one was submitted to cesarean section, and the third delivered spontaneously after external version. The treatment of these 3 patients illustrates the value of modifying treatment to suit the case by careful individualization.

In 2 cases of contracted pelvis a small live baby was very easily delivered when a large baby had been lost from dystocia in the first pregnancy. These patients will probably be what Solomons calls "dangerous multiparas" in future pregnancies. In addition there were 5 other patients for whom skepticism might be entertained as to their obstetric future. If, then, to these 7 are added the 16 who underwent cesarean section, there are 23 who might be classified as "potentially dangerous multiparas," leaving only 10 (30 per cent) for whom normal delivery might be expected in the future.

Many patients returned for a third or fourth delivery, there being 17 additional deliveries of this type. In these cases the conduct of the second delivery seemed to determine the outcome in subsequent deliveries: Patients who were formerly successful in the test continued to deliver successfully through the pelvis, and those who had to submit to cesarean section were all treated by abdominal delivery.

RESULTS

There were 88 deliveries in this series of 33 patients. Two babies were lost in deliveries subsequent to initial stillbirths (Table I), in one case stillbirth being due to dystocia and in the other the infant dying on the eighteenth day after cesarean section from congenital anomaly complicated by urinary infection. The pathologic diagnosis in this latter case was: congenital dilatation of the bladder and multiple abscesses of the kidneys.

before rushing to a section. In the published report of my 92 cesarean sections, now sixteen years ago, I showed that in my experience the only difference between the results of a primary over a secondary operation is that the former has a more placid postoperative course. Results are determined by errors of omission or commission during the period of the test. For a true test to be given, labor must continue until full dilatation is nearly attained. There should be no vaginal examinations, and rectals should be strictly limited to pressing indications.

DR. HUNT (closing).—The duration of the test of labor depends more on the patient's condition than the actual time, also on the type of pains and whether the membranes have been ruptured or not. The psychic factors in these women were not mentioned, yet they were important, for every woman in this series had lost a baby because of hard labor and came to her second pregnancy with a good deal of dread. Even so, I feel we should give most of these women the test of labor when the case warrants it. We sometimes give the woman's husband warning when about to make a test of labor, and in borderline cases the patient and her husband are given some option in selection of the type of delivery, after the relative risks are discussed. Cesarean section has been avoided where possible because of its higher maternal risk.

Cini, Natale: Experimental Research Upon the Influence of Pregnancy Upon the Development of Tar Carcinoma in White Mice, *Folia gynæc.* 33: 273, 1936.

The author states that from the complexity of data, clinical and experimental, it is not clearly understood what influence pregnancy exerts upon the development of malignant growths. With this object in view, the writer undertook the present experimental work upon white mice which had been subjected to carcinoma incited by tar.

The author concludes that pregnancy does not influence proliferative manifestations in the tumors of the white mice, nor does it influence the proliferative manifestations to carcinoma if the lesion was present prior to the pregnancy; but if the pregnancy is superimposed upon simple lesions already undergoing proliferation it facilitates and hastens this process.

The author makes a plea for further research in this problem, which might explain certain apparent contradictions observed in clinical cases.

MARIO A. CASTALLO.

Olsen, A.: Precocious Motherhood, *Acta obst. et gynæc. Scandinav.* 16: 121, 1936.

Among 24,000 labor cases at the Jutland Lying-In Hospital there were 269 patients under seventeen years of age at the time of delivery. Of these, 3 were thirteen years old, 8 were fourteen, 42 were fifteen, and 216 were sixteen years old. Complications of pregnancy and labor were less frequent among these young children than among older women. Of these 269 babies 143 were males and 126 females. Two-hundred fifty-three were discharged alive. Among the very young mothers there was a high incidence of cases where the father of the child was an older man or a close relative of the patient. The author is of the firm belief that extreme youth in pregnancy is not a serious complication or a justification for therapeutic abortion.

J. P. GREENHILL.

the sixteen cases in which the test of labor was successful, the duration of labor averaged eight hours and twenty minutes. The length of trial of labor before failure was evident and cesarean section had to be performed was more than twice this long (sixteen hours and forty-eight minutes). It, therefore, seems that the test of labor should not be too prolonged, especially as a long test increases the maternal, and to some extent the fetal, risk.

Because of the presence of scars from cesarean section, contracted pelves, or pelvic disproportion, 23 of the 33 women in this series may be considered as "potentially dangerous multiparas."

Prenatal care is of special value in the type of case reviewed. Careful and repeated pelvic measurements may be made. Repeated examination as term approaches gives a fairly accurate idea as to whether or not serious disproportion may exist. A more complete history may be volunteered or obtained. Breech presentations may be turned to cephalic by external version, in some cases to allow a test of labor. Labor may occasionally be induced to advantage before term. The physician should take the time to observe and study each case from all angles, so that he will be thoroughly familiar with its important details when the time for delivery approaches.

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DISCUSSION

DR. JAMES R. GARBER, BIRMINGHAM.—The authors have stressed three important things: prenatal care, the problem of labor, and the possibility of delivery. When a case of pregnancy first comes to the doctor, he is somewhat in the position of an architect, and begins to develop a blueprint by careful prenatal observation. He continues to develop the blueprint until the woman is in labor, at which time he must be governed by that unknown quantity which is uterine behavior. The last thing to be considered is why and when to operate. I believe from a practical viewpoint I would rather know the why and when than the art, though that is, of course, important.

DR. RUDOLPH W. HOLMES, CHICAGO.—In different hospitals the stillbirth and neonatal death rate varies considerably, the average being about 7 per cent, but as many are due to congenital causes as to dystocia. The fact that a woman has a difficult first labor, possibly eventuating in fetal death, does not carry any certainty of dystocia in subsequent labors. The first baby had the problem of dilating the soft parts, which are thus prepared for the egress of later children. Many a time I have had the trying experience of a difficult first labor, and later ones were surprisingly easy, even precipitate. Karl Braun, all of seventy years ago, enunciated his dictum based upon many, many thousands of labors that a woman's first baby is usually large: her second the smallest, and only after she has borne seven children is the birth weight comparable to the first child's. A difficult first labor, with or without stillbirth, entitles the woman to careful observation in her next parturition, but no more or no less than should be accorded a woman who has a diminution of pelvic capacity. A test of labor in an abstract sense should always be granted her

hysterectomy following radium, and one had x-ray after a total hysterectomy. Because only 53 per cent of these clinic patients have been traced, the percentage of apparent cures could not be accurate, and is not given.

SUMMARY

From this review of 357 malignancies of the cervix, the following can be deduced:

Periodic examinations must be made. Not only is it necessary for the patient to come to the physician, but he must examine her (and far too often he fails to do this).

The age of patients, after adolescence, apparently has no bearing on the incidence of carcinoma of the cervix except, with everything else being equal, the younger the patient the more rapidly fatal the disease.

Deliveries in this series seem not to have affected the percentage, as 91.37 per cent of patients admitted to the Gynecological Service in this hospital had borne children.

The tragedy of expulsion of a child through an unknown cancerous cervix can be prevented by a careful examination shortly before the expected time of delivery.

When supravaginal hysterectomy is done, the remaining cervix should be given careful attention to insure its reaching a healthy state.

All chronic cervixes should receive proper treatment so as to prevent, as far as possible, their undergoing a malignant change.

The most satisfactory results have been from x-ray and radium therapy.

DISCUSSION

DR. E. F. SCHNEIDERS, MADISON, WIS.—The mental picture of the majority of physicians regarding a case of carcinoma of the cervix is that of a parous woman in the late thirties or forties with a history of atypical bleeding and abnormal discharge. It is therefore of great interest and greater importance to have cited to us the fact that 42 cases of these 357, or 15 per cent, occurred in patients twenty-nine years of age or under, some as young as nineteen years of age. The usual conception has always been that from 95 to 97 per cent of the patients with carcinoma of the cervix had borne children whereas in this series, 27, or approximately 8 per cent, had never been pregnant and 82, or approximately 23 per cent, had never borne a child.

The high incidence of a positive test for syphilis, namely 17.85 per cent, in conjunction with the above cited facts occurring in a series such as this in which cervical infections undoubtedly have been high, lends support to the theory of Beall, Proctor, Regand, and others that infection and inflammation are more important than lacerations and scars as factors predisposing to the development of cancer in the cervix.

I feel that we should commend Dr. Smythe for having presented to us this rather drab picture of a condition which undoubtedly is paralleled in many of our respective communities. Real tragedy is exemplified in the fact that in only 16 cases of Group 1 and 26 cases in Group 2, a total of only 42 out of 357 cases, or approximately 12 per cent, is there a reasonable expectancy of permanent cure. The vast majority of the remaining 315 were doomed as soon as diagnosed, regardless

A TEN-YEAR STATISTICAL REPORT OF CARCINOMAS OF THE CERVIX*

FRANK WARD SMYTHE, M.D., MEMPHIS, TENN.

(From the Gynecological Department of the University of Tennessee)

THIS report is a review of 357 cases of patients with malignant cervixes who were admitted to the Memphis General Hospital from the first of 1926 to the last of 1935. There were 76 white patients and 278 colored ones. This is about the average racial proportion of this Institution's admittances.

Classified anatomically in Group 1 were 16; in Group 2 were 26; in Group 3 were 79; and in Group 4 were 192. In a fifth group there were 26 cases. This group contained those hopeless cases in which there was no chance for any active therapy to aid. In addition to the above 5 groups, the records of 18 cases did not state their classifications.

Cytologically there were only two adenocarcinomas. This is quite a small percentage and may be accounted for by the fact that so many of these cases were in Groups 3 and 4 that, probably, some late cases had lost their tendency to form glands.

The average age was 42.5 years. The oldest patient was eighty-one and the youngest was nineteen years of age. Sixty-six cases occurred after the menopause. There was none before puberty. Of interest were 42 cases in patients twenty-nine years of age and under (14.99 per cent). The average duration of symptoms was six and one-half months, the longest being forty-eight months and the shortest one week. Of these patients 275 had borne children with an average of 4.4 children each. The largest number of children was 23. Twenty-seven (9.63 per cent) had never been pregnant. Sixteen had never borne a child, but had aborted one or more times. Fifty patients (17.85 per cent) had a positive serologic test for syphilis. Five patients certainly had a delivery through a cancerous cervix. One patient was pregnant when the cervical lesion was diagnosed. In 2 cases an additional malignancy was present, one a carcinoma of the breast and the other a sarcoma in the left axillary region. Supravaginal hysterectomy had been done previously in 14 cases. In no case had a chronic cervix received any radical treatment such as surgery, radium, or cauterization.

The active therapy in the first four groups consisted of x-ray and radium. Only 3 patients had operations. Two of these had total

*Read at the Eighth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Detroit, Mich., October 15 to 17, 1936.

for relief of pain associated with carcinoma of the cervix. We soon found that if we operated on all the women with carcinoma of the cervix we relieved only 50 per cent of them. However, if we performed the operation on women who have pain in the lower abdomen, in the back, the rectum, the bladder, or pain associated with rectovaginal and vesicovaginal fistulas, we can relieve almost 100 per cent. Later we resorted to injections of 95 per cent alcohol in the subarachnoid space, and we are pleased to say that in a series of more than 100 cases we are relieving about 85 per cent of these women regardless of the location of the pain. There is one type of pain which cannot be relieved by alcohol injection or by sympathectomy, and this is the pain due to obstruction of the ureter, with resulting hydronephrosis and hydro-ureter. This pain can only be relieved by elimination of renal function either by nephrectomy or by irradiation of the kidney. Practically all other types of pain associated with carcinoma of the cervix can be relieved almost entirely by the injection of alcohol into the spinal column. The technic is simple and every woman who has carcinoma of the cervix and suffers severe pain should have the benefits of this simple injection.

DR. W. H. VOGT, St. Louis, Mo.—I think a paper of this sort is always valuable to a general society particularly, rather than to a gynecologic society. The incidence of cancer is apparently on the increase. Whether there is a real increase or not or whether the apparent increase is due to the fact that we are making the diagnosis earlier, I do not know. At any rate, if we are going to get anywhere with the treatment of carcinoma, we must see the patients early in order to treat them satisfactorily, and to do this we must educate the general practitioner. In the past few years I have been interested in the work of the American Association for the Control of Cancer and have been giving talks throughout the states of Illinois and Missouri. I have been impressed with the lack of knowledge among practitioners in general regarding carcinoma.

There is another thing that the essayist brought out in his paper, that is the occurrence of carcinoma in early life. Too many people still think that carcinoma is a disease of advanced years. In the admissions at the hospital of St. Louis University since April, 1935, of 75 patients with carcinoma of the cervix, we have up to the present date eleven cases of cervix cancer in women ranging from twenty-one to twenty-nine years of age, and all of these with the exception of one were in Group 2 or 3; only one was a Group 1 case. When we see general practitioners treating cases of bleeding and calling it the menopause, where are we going to get in preaching these things in gynecologic meetings? Get the message to the general practitioner that carcinoma is a disease occurring at any time of life. When a woman comes to you who has been under the care of a general practitioner for thirteen months, bleeding steadily and no pelvic examination made, there is need for more education of the general man.

DR. QUITMAN U. NEWELL, St. Louis, Mo.—In 1926 we organized our cancer clinic at Barnes Hospital in St. Louis and have reported our cancer work from time to time, and we have accomplished considerably more in the handling of these far-advanced cases than one would suppose. I do not believe, because a case is far advanced, in Group 3 or 4, that the patient is going to die. Some of them show response to treatment much better than the earlier ones. I believe all patients should be treated just as rigidly, whether they be early or late. In our clinic we treat cervical carcinomas by radium and x-rays and only occasionally we perform a complete hysterectomy and that is on the very early cases. Our statistics show we operate upon less than 5 per cent of the patients applying for treatment. We have a five-year cure of 23.9 per cent.

In the past few years our efforts have been directed toward cancer prevention. We are attempting to educate both the physician and lay public in regard to cancer.

of method or procedure. That such is still the usual picture is suggested by the fact that national statistics show that only about 2 per cent of all cases of carcinoma of the cervix are diagnosed while in early clinical Grade 1. Recent detailed study in Massachusetts, New York, and Pennsylvania has brought forth the information that there is an average delay of twelve months between the onset of symptoms and the institution of adequate therapy and that at least 50 per cent of this avoidable delay is the fault of the physician or physicians involved in the case. It is necessary, therefore, that continued effort be put forth by every available means to educate not only the public but our own ranks as well so as to alter the present situation. That such is possible has been proved in Massachusetts where, after an active educational campaign of six years, it was noted that there was an increase of 36 per cent in the cancer population in the general hospitals of the state. This was a 50 per cent greater increase than the increase in other states. Furthermore, there was no yearly increase in the cancer death rate since 1926, the first time in the history of any state that such results had been achieved. Detailed study showed that the improvement in results was found to have occurred in the accessible cancer groups, one of which is cancer of the cervix.

I do not believe that the final salvage of treated cases will be greatly increased by further developments in therapy, but I do feel that the more universal application of the knowledge now available could almost completely reverse the statistics. Furthermore, I firmly believe that in prophylaxis lies a great opportunity for improvement. I mean thereby the thorough eradication of benign cervical pathology by whatever means indicated, be it cauterization, conization, plastics, amputation or complete removal in conjunction with hysterectomy. We undoubtedly all agree in the logic of the above statements but such is not the general practice by the rank and file of the profession who in reality are still caring for the vast majority of women. That such prophylaxis is effective is strongly suggested by the many thousands of cases reported in which follow-up studies over many years have shown a negligible incidence of carcinoma occurring in cervixes so treated. Microscopic study of tissue removed for benign lesions by Pemberton and Smith in a series of 5,960 cases showed 2.39 per cent of cervix cancer and suggests that in many instances thorough treatment of the supposed benign pathology actually cures occasional cases of very early unrecognized cancer. Certainly this may be the case in so-called "cancer in situ."

Of great personal interest is the fact that in a series of 3,500 cases observed personally during the past twelve years following treatment of the benign pathology there has occurred no carcinoma up to the present time. Also, that in no case of carcinoma of the cervix which has come under our care has there been previous treatment of the cervix. Furthermore, the ratio of cancer of the cervix to cancer of the fundus has been completely reversed in our practice, so that for a number of years we actually have seen more cancer of the fundus than cancer of the cervix. Might this not be due to the fact that for years we have been teaching, preaching, and practicing thorough therapy of benign cervical lesions?

DR. J. P. GREENHILL, CHICAGO.—Most of the papers that have appeared in the literature during the last few years concerning carcinoma of the cervix have dealt, as the one we have just heard, with treatment and results. Notwithstanding the advances made in therapy during the last few years, we have salvaged at most about 25 per cent of the patients. In other words, at least three out of four women with carcinoma of the cervix die of the disease. As the last speaker said, our chief hope lies in prophylaxis and education of the laity and physicians. I arose only to make a plea for the 75 or 80 per cent of women who will eventually die of carcinoma of the cervix. These women sooner or later develop constant excruciating pain. Heretofore we have given these women increasing doses of codeine and morphine. A few years ago I urged the operation known as pelvic sympathectomy

Department of Practical Problems in Obstetrics and Gynecology

CONDUCTED BY WILLIAM J. DIECKMANN, M.D.

THE DIAGNOSIS OF THE SEX OF THE HUMAN FETUS IN UTERO

STUART B. BLAKELY, M.D., BINGHAMTON, N. Y.

THE problem of the diagnosis of fetal sex has always challenged attention, intrigued interest and baffled solution. Among peoples of all ages and areas, effort has been made in vain to bridge that tantalizingly narrow gap between the observer and the child in its mother's womb. A classification of the means and methods that have been employed in fetal sex diagnosis and a discussion of them in some detail, in each group passing from the "superstitions" to the most recent investigations, is the purpose of this paper. A review, however, is subject to limitations.

While the logic of primitive and less remote thought is often vulnerable, it is not inferior to much current today. Regarding the diagnosis of fetal sex, one might fancy that it proceeded somewhat as follows, but not, however, as a line of conscious reasoning. Marked changes from the normal state are evident in the pregnant woman. These changes must be due to the action or influence of the growing product of her conception. These changes vary in different women and in the same woman in different pregnancies. Some of these variations must be due to some difference in the fetus. The only constant obvious difference in the newborn is sex which must also exist before birth. This difference, i.e. sex, must be the cause of at least some of these variations. The male is profoundly different from the female and is considered to be of greater value, strength, and importance. The effect of a male fetus on the mother must be different in kind as well as greater. Therefore the signs and symptoms of a male pregnancy must differ in character and degree from those of a female pregnancy.

The belief that the pregnant woman betrays the sex of her unborn child, especially if male, is very old. With some exceptions, one can only speculate why and when certain of the signs and symptoms observed in pregnancy were singled out and ascribed to the influence of fetal sex. It is tempting to believe that serology and endocrinology were here in the making, an idea not to be followed too far. From the moment that mankind began to fix time, there gradually gathered about the subject a mass of belief, often strangely in agreement in widely separated parts of the world and in widely varying grades of civilization. Many of these ideas and beliefs, popular in origin and frequently hoary with age, were appropriated, rationalized and elaborated by

We must educate the patient to see her family physician at least once each year, and then the physician must make a careful examination of the patient and correct any pathology of the cervix he may find. In this way we will have many less cases of cervical cancer applying for treatment.

DR. E. F. SCHNEIDERS, MADISON, WIS.—In a period of twelve years' time in 3,500 personally conducted cases in which we have cleaned up the cervix thoroughly either by cauterization, conization, plastic, or amputation, we have yet to find the first case that has developed carcinoma. The astounding fact is that in three private hospitals serving the metropolitan area of Madison and surrounding territory, around 75,000 to 80,000 people, that the relationship between carcinoma of the cervix and carcinoma of the fundus has been completely reversed. We are seeing each year fewer cases of carcinoma of the cervix. Dr. Vogt mentioned that carcinoma of the cervix is on the increase. In our particular area it is on the decrease. We are seeing more cases of carcinoma of the fundus than carcinoma of the cervix. I am hoping that it is due to the fact that for many years the profession has been teaching and preaching the necessity of complete and thorough cleaning up of these benign cervical lesions. I am reporting this at this time because we are making a study of a larger area to see if this is merely a coincidence or whether there is something to it.

DR. SMYTHE (closing).—Relative to the question of Dr. Newell, since establishing our clinic, our results, not only in gynecologic patients but in patients with carcinoma of other organs, are definitely better. I agree with him that in these groups where active therapy can be practiced that we should not deprive the patient of a chance to get well. In Group 4 we have a patient cured for seven years and two for over eight years.

Dr. Vogt called our attention to a very important thing which I mentioned in only a sentence in this paper, relative to professional education. I have long since stopped talking cancer to men who have been practicing ten years. I think if we are going to get anywhere as far as our medical knowledge is concerned, we have to get the doctors while they are internes and residents, and get nurses while in training. It is a waste of time to talk to a man practicing ten years who is not cancer wise.

I believe that carcinoma of the cervix particularly is on the increase. Probably it is due to the increase in average longevity of the individual, because the older the patients in the group the more malignancies we have. A relative age incidence of forty-two was mentioned in this particular hospital. I was interested that one doctor mentioned a patient eleven years of age. In this regard, there are cases of cancer in patients six months and seven months old mentioned in European clinics.

Dr. Greenhill brought out a very important point relative to the relief of pain in these cases. I have not tried sympathectomy myself. I have tried removing the hypogastric plexus but have had no success. With alcohol injections merely using 7½ per cent absolute alcohol in distilled water, we have had nine cases of malignancy of the cervix, six of which were hopeless. Four died and three of them had malignant ulcers of the rectum. In eight we had relief of pain. Only two had to have slight sedatives, barbiturates. It does not make any difference whether they form a habit or not because they are hopeless.

I appreciate what Dr. Schneiders said about the percentage of positive Wassermanns in the white and colored. I am sorry I am unable to give him any figures. From this study on which this report is made, I feel that almost all had definitely chronic infection of the cervix. The symptoms, I feel, have been longer in duration on the average than the records show. I am sure the symptoms have been present for over six and one-half months.

ment, for knowledge of the part played by the ovary and the ova in reproduction is not old. Through historic time this idea is found scattered from China to Europe; right-handed signs and symptoms point to a male pregnancy. There is more pain or heaviness or more or earlier movement in, or more prominence of, the woman's right side, if pregnant with a male. The right breast is larger with earlier milk secretion; the right areola is broader and darker with redder, more injected and more projecting nipple. The right eye is brighter, "softer" and more sparkling with wider pupil. All blood vessels on the right side of the body are fuller and beat more forcibly (the sublingual being especially mentioned), and the right pulse is stronger. The right shoulder is lower, and the right thigh thicker. The woman starts off first with her right foot, and supports herself more with the right hand. Salt does not melt on the right nipple, and the right nostril tends to bleed. Many, if not all, of these may be found in the "*De Secretis Mulierum*", a book ascribed to Albertus Magnus (1193-1280), which was widely used in the scholastic time of medieval medicine.

While right-sided signs and symptoms are no longer valued in fetal sex diagnosis, a bit of the old belief still lingers in the theory of the ovarian or ovular determination of sex. The idea that sex is determined by the egg still lives and will not die, and among men of scientific training. As a matter of fact, the last word on the subject has not been spoken. Otto Schoener published his theory in 1909 and his results in 1924 and 1925. It has given rise to a large volume of German literature. Schoener held, and still holds, that the right and left ovaries alternate continuously in their activities (an idea suggested by Bischoff in 1844); that the human ovum possesses its sex "*Anlage*" before fertilization; and that the sex "*Anlage*" changes, possibly better said, appears, in each ovary in the following sequence: right ovary, male; left ovary, female; right ovary, male; left ovary, female; right ovary, female; left ovary, male. The cycle is repeated *ad infinitum*. E. Rumley Dawson proposed the hypothesis that male and female determining ova are discharged from the ovaries alternately, male from the right and female from the left. Both these men claim that, after the first pregnancy, it is possible to quite accurately foretell the sex of future children by a careful history of the menses (actual and missed), assisted by the palpation of an enlarged tender ovary due to the presence of the corpus luteum of pregnancy. The difficulties of these theories are quite apparent; e.g., menstruation is not always associated with ovulation nor vice versa, and the sex of children after unilateral oophorectomy does not always conform to the rules. Through many years of observing pregnant women, I have never been able to determine any right-sided signs or symptoms peculiar to a male pregnancy, nor evidence of either definitely alternating ovarian activity or of the ovular determination of sex. It is probably safe to deny their existence, though dogmatic statements about the physiology of sex are dangerous.

GROUP 2

The position, outlines, attitude and activities of the fetus during pregnancy and labor.

Hippocrates held that the boy moves in the womb at three months, the girl at four. This idea, with variations in the actual number of the months, was once widespread. It was also thought that

ancient and medieval medicine. With the rise and growth of new ideas in anatomy and physiology in the sixteenth and seventeenth centuries they were largely dropped by the science of the day, to revert to and to become again, for varying periods and in varying forms and degree, the property of folk belief on the subject. Through the years these colorful ancient concepts have gradually faded in the West until among us today, in marked contrast with other obstetric superstitions, only the faintest traces exist. Until shortly after the middle of the last century nothing of scientific value or resulting from scientific effort (as we understand science) was added toward the solution of the problem. But those old folk beliefs, call them superstitions if one will, about the means and the possibility of foretelling the sex of the unborn child must not be unceremoniously cast aside. They are worthy of study and of more than a tolerant or amused interest. Age-old wisdom merits respect.

All means that have ever been used to diagnose fetal sex may be placed in two great classes: supernatural and natural.

The means employed in the first class were the prophetic interpretation of numerology (still existing as late as the sixteenth century in countries as far apart as China and Italy), astrology and dreams; of the examination of the entrails of sacrificed animals and of the flight of birds; of "ordeals"; of chance happenings and occasions; and of magic formulas and other procedures. Material on this phase of the subject can be found in the first volume of Ploss-Bartels. It is interesting that the use of strictly supernatural means to diagnose fetal sex was never persistent or extensive, compared with the second class. I have not met nor heard of a survivor. Legendre records a French folk belief in a curious mixture of lunar influence and numerology.

The second class, comprising the natural means to diagnose fetal sex, from time out of mind to the very present, may be divided into three broad groups.

Group 1. The supposed origin of the male from the right side of the uterus, the female from the left; and the changes in the right side of the pregnant woman's body ascribed to, or imagined to result from, such origin.

Group 2. The position, outlines, attitude and activities of the fetus during pregnancy and labor.

Group 3. The effects of a male fetus on the total maternal organism; i.e. the reactions of the female body to the introduction therein of a male element. This is the largest and most important group.

GROUP 1

A notion of antiquity was that the human uterus consists of right and left cavities, as is normal in many animals which were the chief source of the ancients' ideas of anatomy. Since the right side has always been considered the stronger, superior and "holier" side and the male the stronger, superior and more valuable sex even in its mother's womb, it followed that the male must develop in the right side of the uterus, the female in the left. Hippocrates taught that "The male fetus is usually seated in the right, the female in the left side of the uterus." After it was known that the human uterus is not normally duplex, the idea became current that the male came from the right ovary, the female from the left. This must have been, however, a comparatively recent develop-

greater demands on the pregnant woman. There is claimed to be more iron in the male placenta; more adrenalin in male urine, and therefore (?) more in the urine of a woman pregnant with a male child. It is said that midwives in the Philippines used to prophesy the sex of the unborn child by the reaction of the pupil of a male dog's eye into which had been dropped some of the pregnant woman's urine. Thinking along this line, I observed the pupillary reaction of twenty-five pregnant women on whom the Bercovitz test of pregnancy was done, to see if the contraction or dilatation of the pupil bore any relationship to the sex of the fetus. The results were negative.

The second idea, that the reaction of the pregnant woman to a male fetus is *qualitatively* different than to a female fetus, is very old, runs as a common thread through most of the ancient methods of sex diagnosis, and is the basis of nearly all modern efforts to solve the problem. Hormones can and do pass the barrier of the placenta. Profound changes are produced in the pregnant woman's organ growth, circulation, skin, glands, etc.; she is often rejuvenated. Their origin must be in the fetus, a source of additional, possibly new and different, possibly even antagonistic hormones. If the fetus dies, these changes retrogress. There is no question but that a male hormone (using the singular for convenience) exists. There is some question when and in what quantity this hormone is first produced in the fetus. There is a still larger question if the male sex hormone, by circulating in the maternal blood stream, induces or can induce recognizable specific changes in the mother's body, by acting as an antigen with the production of "antibodies" or by some hormonal effect. Every cell of the male fetus must differ from the female cells of the mother. The mother has no organ homologous with the fetal testis or the fetal tissues that produce male sex hormone. There is probably no antagonism between sex hormones as such, i.e., they do not neutralize each other when mixed together. But there does appear to be some sort of antagonism, direct or indirect, between the specific hormone of one sex and the specific hormone producing organs or tissues of the opposite sex. Moore and Price reject Steinach's and other's ideas of sex hormone antagonism; they admit that certain facts do point to such action, but claim that the effect is indirect through the hypophysis. But compare the production of sterility by the parenteral injection of semen or even its vaginal absorption; the production of agglutinins against spermatozoa; and the occurrence of freemartins and other phenomena to be discussed in the immediately following paragraphs. Does the introduction of maleness, e.g., a male fetus, into the female body produce quantitative or qualitative changes that can, possibly one might add, some day in the future, be recognized by the clinician or the laboratory worker? Is there any evidence that a male pregnancy has an effect on the mother, different in degree or character from that of a female pregnancy? In the attempt to answer these questions, let us examine further evidence which is closely bound up with the inescapable idea of some sort of sex antagonism.

1. Ancient belief. This must be neither lightly regarded nor summarily ignored. The remarkable agreements of such beliefs among peoples widely separated in time, place and culture arrest attention. Somewhere in the welter, to be found some day by some seeing eye, may be a little, or *the* little, grain of golden truth. Not everything that we cannot prove scientifically is improbable.

labor was slower with a female child. These conceits are entirely consistent with the belief in male superiority. The girl was supposed to be born "face-up," looking at the rib whence she came; the boy, "face-down," looking at the earth whence *he* came, a bit of Genesis or reminiscent of the usual position at coitus.

In this group belong two modern "natural" means that have been employed in the effort to solve the problem: the x-ray (two procedures) and the rate of the fetal heart. Roentgenologists agree that the ossification of the skeleton of the female is more advanced than that of the male throughout intrauterine life; it has been suggested that this fact might be utilized to foretell fetal sex. Visualization of the fetus in utero (including the outlines of the soft parts), by rendering the amniotic fluid opaque through the injection of strontium iodide into the amniotic sac, occasionally permits the diagnosis of fetal sex, if a true lateral view of the breech is obtained (menees).

In 1859, on the basis of a study of one hundred cases, Frankenhaeuser suggested that fetal sex might be determined by the rate of the fetal heart in the last three months of pregnancy, a persistently slow rate (averaging 124 or less a minute) indicating a boy, and a persistently more rapid rate (averaging 144 or more a minute) a girl. A large number of observations have been made with a corresponding literature. If the male fetal heart is slower, it must be due to some peculiar influence of male sex itself, maleness per se, for which I know of no evidence; or because the male is heavier or bulkier, but the average difference in the birth weights of the sexes would seem to be too slight to have much effect; or the result of some hormonal action, as yet unknown. It is generally conceded today that the method is of no, or at least of very little value, if for no other reason than that the usual fetal heart rate falls between the figures given and so into the uncertain class. Many of the laity express a wistful faith in it. Some physicians, for unworthy or obscure reasons, encourage this faith by professing, at least not denying, the same. Nevertheless, it may lay claim to have been a really intelligent effort to solve the problem.

GROUP 3

The effects of the male fetus on the total maternal organism, cells and organs, their functions and secretions.

In pregnancy, mother and child are a biologic unit. If the mother's own hormones produce well-recognized phenomena, why may not added fetal hormones (which she surely receives) alter these phenomena in degree or character? If the male fetus introduces into her economy new or "foreign" hormones, why may these not alter her response; and, if harmful (as we know they may be), why may they not meet hormonal or humoral resistance (protective?)? The maternal response to pregnancy may be physical, or biochemical (using the term in a broad sense), or both. Her reactions may be quantitative, or qualitative, or both. A discussion of these two possible types of reaction now follows.

Aristotle held that, since the female is on a lower developmental plane, a female pregnancy has less effect and makes less demand on the maternal organism than does a male pregnancy; that there is greater body warmth in a male pregnancy and therefore a better circulation; and that on these as a basis the diagnosis of fetal sex is possible. Some observers today agree with Aristotle that a male pregnancy makes

anastomosis does not occur in man. Sir J. Y. Simpson collected the married history of 123 women born co-twins with males and found that only 11 had no offspring.

4. Fetal malformations. As a whole, there are probably more male than female fetuses that are malformed. Dr. D. P. Murphy of Philadelphia, in a personal communication, says, "If you were able to secure figures on the sex ratio of 500 cases of any given type of defect you might well find . . . that the defects in most cases afflict the two sexes about equally." But the available figures show strange sex ratios of congenital deformities. Curiously enough, deformities of the brain and cord, and of congenital hip dislocation are much more common in the female. M. S. Michel of Minneapolis reported in 1928, 57 cases of craniorachischisis, of which 85 per cent were female; Malpas, 44 cases of anencephaly with 70 per cent females, and 80 of hydrocephalus and spina bifida with 57 per cent of that sex. Of 5,494 cases of congenital hip dislocation, 84 per cent were females. On the other hand of 3,309 club feet, 65 per cent were males. Of 507 cases of harelip-cleft palate gathered from various sources, 55 per cent were males. Ballantyne reports the sex ratio of his malformations as follows: iniencephalus, 1 male to 21 females (5 per cent males); anencephalus, 10 to 30; genal fissure, 41 to 26; harelip, 180 to 118; diaphragmatic hernia, 47 to 20; preauricular appendages, 21 to 12. These percentages are approximate. He states that there are more female cyclopias and united twins; but more male urinary umbilical fistulas and polydactylism; of extroversion of the bladder, male:female::"6 or 7:1"; of transposition of viscera, "2:1." I have not been able to secure much evidence for the suggestion that most pseudohermaphrodites are primarily males, the course of whose early sex differentiation has been altered by the antagonistic sex hormones of the mother. Such evidence would be very interesting. In 980 cases of placenta previa the male-female sex ratio was 124:100. While fetal malformations are not good witnesses to any distinctive effect of maleness on the maternal organism, still sex in some way would seem to play a part in their production.

5. Relation between male pregnancy and toxemia. An old belief, still alive, was that the pregnant woman vomits more if her baby is a boy. v. David suggests that the cause of the vomiting is something transmitted to the child from the father that is foreign to her blood; that the more the child resembles the father, the more the mother vomits; and that the pigmentation of the mother parallels that of the child. In all this, no direct mention of sex diagnosis. Herrmann reports in 1,442 cases of eclampsia a ratio of male to female children of 122:100 (normal ratio, 105:100); in the last four months of pregnancy, this ratio rose to 156:100; and in those eclamptic individuals with twins, to 173:100.

6. Serologic studies. These, while not conclusive, evidence a difference between male and female blood and serum greater than that afforded by chance.

The foregoing would seem to justify the conclusion that the introduction of the male element into the female body does produce effects. The mechanism by which the male fetus is protected against the antagonistic sex hormones of the mother is, at times, more or less broken down. Sufficient means and knowledge are not yet at hand to definitely recognize such effects and permit practical sex diagnosis.

2. The frequency of male abortions. The ratio of male to female abortions is at least 150 to 100. The cause must be in the "fruit." This may be the reason for nature's prodigality with male pregnancies, because so many are destroyed by some unfavorable reaction to their presence in the maternal organism. Some women seem to abort all male conceptions, carrying only female to term; the reverse, at least in my personal experience, is rare. Male stillbirths are also more common, even after discounting the usual causes for this condition and the hazards of male birth itself. Cases of unexplained and of "habitual" death of fetus near or over term are 80 per cent males. The excess of males among abortions and stillbirths is greatest during the first and last third of pregnancy; this may have something to do with the development of the interstitial cells in the fetal testis.³⁴ While it is true that there are more male than female twins (1043:1000; the ratio in single births, 1050-60:1000), due to the great preponderance of male pregnancies, the prenatal mortality of male twins is higher, and "as the number of individuals to a birth increases the relative proportion of males to females decreases." Nichols, who collected statistics of over 700,000 pairs of twins, has pointed out that the ratio of males to females decreases from 1059:1000 in single births to 548:1000 in quadruplets. The Dionnes are girls, and so are most quadruplets of press renown. In sheep there are over twice as many female as male triplets. For opposing view consult A. S. Parkes.

3. The occurrence of freemartins, in cattle and more rarely in other animals. A bovine freemartin, probably meaning "farrow heifer,"¹³ is the female co-twin of a normal bull calf; the female of two-sexed twins. Cattle breeders from Roman times have known that such females are usually sterile, 87 per cent or more (some observers claiming even 100 per cent) instead of the normal incidence of less than 10 per cent. Lillie has shown beyond all question that a freemartin is a "blighted" female calf fetus with undeveloped or deformed sexual organs (usually internal only), and often with more or less male characteristics due to saturation with antagonistic male sex hormone from its co-twin which interferes with the normal female development. This is possible, and occurs only when the chorionic or placental anastomosis between the binovular twins is early and extensive. Either the male shows an earlier sex differentiation and an earlier sex hormone production than the female, or the male sex hormone is more "powerful." The former of these ideas suggests that sex is not absolutely determined by the spermatozoon but is profoundly influenced by environment; the latter, again, the ancient thought of male superiority. Williams, in a personal communication, reports "Quintuplets with two males and three asexuals; triplets, one male and two asexuals, twins, one male and one asexual. Ten individuals with 4 males and six sexless. There were 8 abortions and two viable young (the twins)." Hartman believes that the process can be reversed in which a male co-twin is sterilized and made more or less asexual or intersexual (sexual intergrade) by the female. He calls these "reciprocal freemartins," and rather believes that both types do occur in man and may explain some cases of intersexuality (Novak). Contrary to a belief once held in rural England, no diminished fertility in the female of two-sexed human twins has been observed because a comparable placental

There was a curiously widespread idea that the milk (sometimes specified as of the right breast) of a woman pregnant with a male was "tough" and thick. The test was to drop or squirt the milk onto a smooth surface, e.g. glass, a sword or a heated metal plate. If it remained conical or "stood like peas" or clotted, a male pregnancy was indicated; if it spread out or flowed off, a female. If some of the milk dropped into clear water or urine fell to the bottom, a boy was to be born; if it floated or dissolved, a girl. Another test was to knead the milk with meal into a small loaf to be baked over a slow fire; if it shriveled up or burned, a boy; if it "puffed up," a girl. It appears that these tests were occasionally, but much more rarely, applied to blood and urine. Much of the foregoing is not strange to primitive thought about sex.

With the two exceptions, marked vomiting which is still occasionally spoken of as a sign of a male pregnancy and sport with the pith ball, possibly the only other "natural" means to diagnose fetal sex, existing in popular thought today, are the changes that "old women" think they discern in the shape and appearance of the pregnant woman's abdomen and back. There is by no means complete agreement; but, in general, a hard, prominent, "high" and rounded abdomen and broad hips and back bespeak a male pregnancy. An abdomen sometimes described as "egg-shaped" is stated to indicate a female pregnancy. The origin and age of these ideas is not definitely known; some may have a phallic significance. While I have not been able to arrive at any definite conclusion from many wearied questionings and many observations, I am not willing to dismiss the matter as entirely without foundation. Possibly, an endocrine truth may be embodied in this popular persistent belief.

To digress a moment into veterinary medicine, cattle breeders have stated that the calf is more likely to be a male if the front quarters develop first in pregnancy and if the cow goes over term.

In modern times, excepting Frankenhaeuser's fetal heart study in 1859, there is no evidence that either science or scientific medicine concerned themselves seriously, if at all, with the diagnosis of fetal sex in utero, until toward the end of the first decade of this century. Since then the problem has been attacked from many angles. Those in Groups 1 and 2 have already been mentioned. In Group 3, serology and endocrinology have been the means employed; and the efforts, in the main, have followed the two ancient lines of thought about the effects of a male fetus on the maternal organism, the one, that they are quantitative; the other, that they are qualitative.

Excepting unsuccessful attempts to demonstrate a higher pH value in the blood of a woman pregnant with a male or a higher basal metabolic rate, the Manoilloff test is possibly the only modern example of the first idea, though not intentionally so in origin.

In ancient thought all things had sex, which the study of language amply illustrates. The alchemists held that the elements were male and female. E. O. Manoilloff, the Russian scientist, has revived that concept. He claims to be able to distinguish between male and female tissues and secretions (first in 1920), to determine the sex of the fetus by examination of the pregnant woman's blood, to diagnose the sex of plants, and to separate male from female minerals. He claims sex differentiation from stone to man. As a matter of fact, female sex hormone

The ancient ideas of the qualitative effects of a male pregnancy on the mother comprise a large number of "natural" means to diagnose fetal sex. Hippocrates said that "a woman with child, if it be a male, has a good color; if it be a female, she has a bad color." Ambrose Paré quoted this with approbation. It is remarkable that the agreement was so general that the appearance of the woman during a male pregnancy was good, with a sense of well-being. The face is brighter, the color better, the skin clearer; she is cheerful (Arabian), happy (Indian), and untroubled (Jewish). Many of these may be explained by the belief that the increased heat production, held to be associated with a male pregnancy, quickened the circulation and heightened metabolism; suggestion and wishful thinking may have played a rôle; finally, however, with these as with many other ancient ideas about fetal sex diagnosis, we may be standing on the edge of an unexplored field of endocrinology.

Freckles, pigmentation, and vomiting were sometimes stated to indicate a boy, though Hippocrates held that freckles meant a girl. While "liver spots," a blotchy skin and a bad or pallid color were usually interpreted to mean a girl, pigmentation in general pointed to a boy. There was widespread belief that *lack* of pigmentation of the linea alba below the navel meant a girl. The endocrinologists have here food for speculative thought. It was also an old idea that the desires of the pregnant woman are an expression of the desires or will of the fetus (and so helpful in fetal sex diagnosis), and that these fetal desires are often expressed in dreams. In India, if the pregnant woman dreamed of men's food, the baby would be a boy; in Russia, dreaming of a spring or well meant a girl; of a knife or club, a boy (Freud?). There was no agreement in the interpretation of changes in sexual desire during pregnancy. Incidentally, the subjective sensations of the pregnant woman have never been considered of great value as evidence in fetal sex diagnosis; but this may be another entirely unexplored clinical field.

The most interesting "natural" means in Group 3, anciently used to foretell sex, have been the supposed effects of the fetus on the pregnant woman's excretions: urine, milk, and sputum. A generation ago no one would have dreamed that the diagnosis of pregnancy was possible by an examination of the urine. But in ancient Egypt about 1350 B.C., according to the *Berlin Medical Papyrus*, both pregnancy and sex could be determined by this means. "To see if the woman is pregnant or not pregnant: barley and wheat are moistened daily with the woman's urine, like dates or pastry in two bags. If they either generate, so will she give birth; if the wheat germinates, so will it be a boy; if the barley germinates, so will it be a girl; if they do not generate, so is she not pregnant." The idea had found its way to Europe by the seventeenth century. "Make two holes in the ground, in one place some wheat, in the other barley, wet with the woman's urine and cover with earth. If the wheat sprouts first, the woman has a male fetus; if the barley first, a female." The test is mentioned in the old English book, *The Experienced Midwife*. Manger repeated the experiment in 1933 and reported 80 per cent correct prognostications, but his findings have not been corroborated. If any difference in the effect of male and female pregnant urine on the growth of these seeds *does* exist, it must depend on the presence of some substance produced, directly or indirectly, by the fetus.

to be of value in fetal sex diagnosis. Of course, it can be argued that spermatogenesis is not a function of fetal life; that it is not known to what degree "maleness" is dependent on the external secretion of the testis; and that the serums might have been from patients already sensitized. References to other work of this character have not been found.

Complement fixation tests for diagnosing fetal sex were employed by Petri, using extract of fetal testis, inactivated navel blood, and fresh guinea pig complement. All gave hemolysis. Others have tried to solve the problem by this method which would seem to merit further investigation. I had a personal interview with an individual who believed that he had succeeded by this method. The New York Academy of Medicine scheduled for the Section of Obstetrics and Gynecology on April 28, 1925, a paper by Isaac Fried, M.D., entitled "The Serodiagnosis of the Sex of the Fetus During Pregnancy," "by invitation." The paper was withdrawn before the day of the meeting arrived. The author's interesting, but not at all convincing, complement fixation test, featuring a very complicated, possibly even fantastic, antigen, was published in the *Medical Review of Reviews*, August, 1924. He claimed 100 per cent correct prognostications.

The principle of the Abderhalden test [the formation of protective (?) ferments against living foreign proteid] has been extensively used in trying to foretell fetal sex, using testis instead of placenta. Waldstein and Erkler in 1913 reported positive results from the action of pregnant serum on testis, but they considered it due to previous semen absorption and made no mention of its possible use in fetal sex diagnosis. In 1914 Franz Lehman first suggested that fetal sex might be determined by a modification of the Abderhalden test. Later, he attacked the problem himself. Koenigstein of Schauta's clinic in Vienna in 1913 found that there was more destruction of fetal, infant, and steer testis by male than female pregnant serum. In 1917 Kraus and Saudek of Brumm published their stimulating work done in 1913 and 1914. They employed carefully prepared (kosher) steer testis and pregnant serum, claiming nearly 80 per cent correct prognostications. Schaefer of Bumm's clinic tested fetal and adult human testis and calf testis with pregnant serums; the best results were obtained with fetal testis, but the conclusion reached was that the test was not reliable. The most determined effort to use a modified Abderhalden test in fetal sex diagnosis was made in 1924 by Luetlge and v. Mertz at Sellheim's clinic, the scene of Abderhalden's original work. For a "substrat" they used carefully prepared bull testis (later, a commercial product free from aminoacids), which was incubated with the serum to be tested. The high molecular proteids were precipitated from the filtrate by alcohol, using this instead of dialysis. After further filtration, the final fluid was tested for split proteids, presumably produced by the antitesticular ferments in the male pregnant serum, by a ninhydrin color reaction. In 1925 I spent a day in their laboratory, and, later in the same year, tried to duplicate their results at the Kilmer Pathological Laboratory. Our first seventeen serums were diagnosed (?) correctly: the next eight were wrong. A large literature for and against the method and its accuracy exists. The originators claimed over 78 per cent, even up to 98 per cent, correct prognostications. Those interested may consult their book. The optical interferometric method of Loewe-Zeiss has been used by many investigators, especially P. Hirsch, to test the serum after incubation, quantitatively.

has been recovered from minerals. Regarding fetal sex diagnosis, Manoilloff believes that a specific hormone from the fetal testis, or from the whole organism of the male fetus, passes into the maternal blood and changes its reaction. To the specially prepared blood is added an oxidizing agent, a reducing agent, an acid and an indicator. The result is determined by the absence or presence of a color reaction. The idea of many investigators is that this test represents an oxidation-reduction process, of which the former predominates in the male, the latter in the female; that the substances involved parallel the metabolic rate; and that the test is one of metabolic rate or level. It is quantitative, and not sex specific. We are back again at the beginnings; one mark of sex is a difference in metabolic rate. Many modifications of the test have been made and its chemistry is complex; the necessary technic is delicate and subject to much possible error. Manoilloff's claim of 80 per cent correct prognostications would seem overoptimistic.

A possible immunity reaction between the pregnant woman and her unborn male child has been the basis of most of the efforts of serology to solve the problem of fetal sex diagnosis during the past twenty-five years. It follows the second ancient idea that one of the effects of a male fetus on the maternal organism is a qualitative change, caused by the elaboration of specific substances, and is predicated on the four following assumptions: (1) Even early in pregnancy there is sex differentiation in the fetus (morphologically, sex can be distinguished in a fetus 20 mm. long and six weeks old), which becomes more marked as pregnancy advances. (2) The male secretions, i.e. the "maleness," of the fetus passes into the mother's blood. (3) These secretions, being "foreign" to her body cells and their products, act as antigens. (4) As a result the mother produces "antibodies" against the invading "foreign" substances. The demonstration of these hypothetical "antibodies" has been attempted by precipitin reactions, agglutinations, complement fixation tests, activity of ferments and allergic phenomena. The possibility must be constantly borne in mind that all such serologic tests may be invalidated by previous sensitization.

Petri experimented with precipitin reactions between cow and steer serums and steer testis extract. Both serums gave precipitations when overlaid with the steer testis preparation, though stronger with the steer serum. The same results were obtained when antitesticular serum (from rabbits injected with this testis preparation) was tested against cow and steer serums. Even after fractional precipitation of this antitesticular serum by cow serum until precipitation ceased, the addition of steer serum still gave a reaction. By these and other reactions he was able to determine the sex of serums in many cases, but the test was not dependable. Abraham in 1912 to 1914 conducted an extensive series of precipitin experiments. He injected rabbits with male and female pregnant serums and with male and female nonpregnant serums. Combinations and dilutions of serum from these sensitized rabbits were tested for precipitation against serums similar to those injected. His results were also not conclusive. His work stimulated investigation and his article contains an extensive bibliography.

The agglutination or immobilization of animal and human spermatozoa by the serums of pregnant women has been briefly investigated by me. While the degree of the reactions varied from what might be called complete to none whatsoever, even the markedly positive cases did not seem

In the second group are the beliefs that the physical attributes of the fetus during pregnancy and labor differ in the sexes.

In the third group are the beliefs that the male fetus, through its secretions, affects the mother differently than does a female fetus. These differences in effect may be of degree or kind, and there is some evidence that they do exist. Sufficient knowledge and means are not now at hand to recognize these differences for practical use. This group is the largest.

The ancient beliefs about the diagnosis of fetal sex have almost entirely disappeared, but are of interest, for ancient thought is the basis of nearly all modern attacks upon the problem.

Modern investigations of the problem have one or more representatives in each group. In the third group serology and endocrinology have been the means employed, with encouraging results.

That much thought has been expended and much work done in this broad field, with its many converging paths of research, is evidenced by the appended bibliography, which is by no means complete.

Neither clinical observation, nor serology, nor endocrinology has solved the problem of fetal sex diagnosis.

CONCLUSION

The correct prognostication of fetal sex would satisfy a great curiosity and answer the pregnant woman's age-old question. It is true that it would not have great practical value. Research along other lines might well produce more solidly beneficent results. It may be true that such diagnosis, if possible early in pregnancy, might increase the incidence of induced abortions, though this does sound a bit timorous and far-fetched. The parents made unhappy by knowing beforehand what they were going to have might easily be outweighed by those rejoicing in the knowledge that they would have a child of the sex they most desired. Its discovery might be exploited by the unscrupulous, as was salvarsan in its early history. All these and other objections have been raised. But the fact remains that no permanent harm has ever come by making the way of truth wider or smoother or straighter, or by pushing it a little farther. The diagnosis of fetal sex in utero is one of the unsolved problems of obstetrics. As such, it will remain a challenge. Some day, some eye will see clearly what men have, as yet, seen only through a glass darkly; or some laboratory worker will present the answer to us face to face. Clinical observation may come into its own some day, and what lies ahead in hormone study is not even dreamed of. The problem may still be solved.

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Allergic skin reactions have been the basis of a number of attacks on the problem of fetal sex diagnosis. Lehman tried skin inoculations with extract of animal testis; Koenigstein cutaneous injection of testicular extract in pregnant animals and pregnant women. Their results were not definite. Human semen and extracts thereof, preparations of testis (both animal and human) and male fetal blood serum have been employed in skin tests on pregnant women by scarification and intradermal injection. The reactions have been sometimes negative, sometimes slightly to markedly positive, frequently bizarre. While the results have been too conflicting to permit definite conclusions as to their ultimate value in prognosticating fetal sex, they have been without question better than those afforded by chance. The most recent report is by Davis who injects intradermally a stock testicular extract, grades the test by the resulting wheal and reports between 80 and 90 per cent correct findings. It is a hope that all these puzzling skin reactions may be better understood when the workers in allergy shall have been able to put their house in order.

Although fetal sex hormones must be the primary cause of any differences that may exist in the effect of fetal sex on the pregnant woman, endocrinology to date has disappointed high hopes of solving the problem of fetal sex diagnosis. The male and female sex hormones are closely related chemically, their differentiation in the blood is difficult, and "both male and female stimulating substances can be extracted from both male and female urines" (personal communication from Dr. Carl R. Moore). With the cooperation of Mr. Jesse Briggs of the Kilmer Pathological Laboratory, I have carried on some observations of the number and prominence of the developed follicles in the Friedmann test, to determine any relationship to the sex of the child. The number of observations has been too small to warrant any conclusion. Dorn and Sugarman injected intravenously into immature male rabbits, whose testes must be in the inguinal canals and not in the scrotum, the urine of woman pregnant in the last trimester of pregnancy. If later examination of the testes of the animal showed increased vascularity and cellularity and beginning spermatogenesis, they believed that they could conclude from their series of cases that the woman was pregnant with a female fetus. They thought that they had discovered, in the urine of women carrying a female child, a true and hitherto undiscovered sex "hormone which can stimulate the cells in the testicular tubules of the pubescent male rabbit and cause a precocious development." They claimed 94 per cent, 80 out of 85 cases, correct prognostications. Other workers have not been able to duplicate their results. Mathieu and Palmar cite numerous references, record the results of their own investigations which did not succeed in accurately diagnosing fetal sex, and indulge in some interesting speculations. It was inevitable that the hormone test for pregnancy would be employed in the attempt to solve the problem. It is encouraging to remember that endocrinology is the merest infant in the world of medicine.

SUMMARY

All efforts ever made to diagnose the sex of the human fetus in utero may be placed in three groups.

In the first group are the beliefs that the male comes from the right side of the uterus or the right ovary, and that male pregnancies cause right-sided symptoms in the mother.

Department of Book Reviews

CONDUCTED BY ROBERT T. FRANK, M.D., NEW YORK

Review of New Books

Gynecology

Dr. Jameson has given us a delightfully written account of the early customs and manners in obstetric practice and teaching, as well as depicting the rise of the recent specialty of gynecology, in this newest example *Gynecology and Obstetrics*¹³ of the series of histories which have been appearing under the title of "Clio Medica."

Evidently in obstetrics as in other branches of science little that we think is new is really new, for as the author carries us through the traditions and customs of the early period and those of Greek and Roman times we find many suggestive allusions to methods which are not far different than those of the present day. What a commentary it is on the profuse output of the obstetric and gynecologic texts of this era to read that the famous "Rosengarten" of Eucharius Roslin was the first obstetric textbook to be issued in fourteen centuries.

The modern period of obstetrics begins with the work of Mauriceau, van Deventer, and Portal, and from this we are gradually carried to the development of the modern maternity hospital. One of the most interesting chapters in the book is the account of the Chamberlain family, and the development of the obstetric forceps. The story of puerperal fever is no less interesting, especially in view of the fact that sepsis still remains the scourge of modern maternity. It is especially pleasing to note the large part which American surgeons took in the development of gynecologic technique. The obstetric classics, in many instances consisting of records of the original procedures and discoveries, are reviewed. This most interesting contribution to the history of obstetrics and gynecology deserves to be widely read.

—Philip F. Williams

Gynecological Operations,¹⁴ and their topographic anatomic basis, by Martius, gives a survey of the gynecologic technique as practiced at the Goettingen Gynecological Clinic. In his foreword the author promises to give a short operative gynecology, mainly based on topographic anatomy, designed for both students and physicians, together with a brief text giving the pathologic background. It may be said that he has succeeded in performing this difficult task in an almost faultless fashion.

The text is illuminated by 404, chiefly colored, halftones, clearly drawn and well executed. I know of no other operative gynecology which is more clearly designed or better illustrated. Throughout, the author uses conservatism and good judgment for indications of the operation. The topographic anatomy is not concentrated in one portion of the book, but distributed with each operation so that it is immediately available during the reading of the text. The schematic drawings are of utmost value.

¹³*Gynecology and Obstetrics*. By Edwin M. Jameson, M.D., Surgeon, General Hospital, etc., Saranac Lake, N. Y. 170 pages with 5 illustrations. Paul B. Hoeber, Inc., New York, 1936.

¹⁴*Die Gynaekologischen Operationen*. Von Professor Dr. Heinrich Martius, Direktor der Universitäts-Frauenklinik in Goettingen. 396 Seiten, mit 404, zum grossen Teil farbigen Abbildungen und Bilderreihen. Verlag von Georg Thieme, Leipzig, 1937.

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The case which speaks most highly in favor of this method is that well-known one of Wagner who performed the operation of Schubert in a patient in whom the vagina had been entirely destroyed by postpartum sepsis. Later this patient delivered 3 children through the newly made canal.

The author has made no attempt to gather the literature in order to determine the actual mortality following his type of operation.

—R. T. Frank

Mathey-Cornat has covered *Gynecological Radiotherapy*¹⁸ in a well-written monograph. There is a short introduction on technic and dosage, cautions to be employed, the dangers and bi-effects which may be encountered.

Radiotherapy is recommended for endometriosis, both pre- and postoperatively in the treatment of fibroids. He prefers daily fractional dosage extending over twenty to twenty-five days. He wisely excludes any doubtful cases and also young patients in whom myomectomy could be performed. He concludes that failures are rare unless based on the wrong diagnosis.

For uterine bleedings in the young as well as for permanent sterilization, his choice is radium in preference to x-ray. In tuberculosis of the genitals his results have been good. As most other men in this field, he believes that operable corpus carcinoma should be treated by surgery.

Both for sarcoma of the uterus and for chorionepithelioma as well as for ovarian malignancies, he advises only postoperative radiations. For carcinoma of the breasts, pre- and postoperative radiation is used.

The monograph is well illustrated. It incorporates in its pages much of the world's literature referring to the subject.

—R. T. Frank

The seventh volume of *Ergebnisse der medizinischen Strahlenforschung*¹⁹ is the first one to appear since 1933. It contains a fund of interesting material. The 12 articles with the exception of 2 from Zürich and 1 from Czechoslovakia, are all from Germany. The first one deals with dextroversion of the aorta, a condition rarely giving symptoms, usually an accidental x-ray find but sometimes causing esophageal or tracheobronchial disturbances. The next takes up Hand-Christian-Schüller disease. One hundred and forty cases have been reported in the literature. The defects in the membranous bones, diabetes insipidus, and exophthalmos, as well as xanthematosis, give a clear-cut clinical picture. Good effects are reported from x-ray therapy.

Osteosclerosis fragilis generalisata, the so-called Albers-Schoenberg "marble bones," is a disease existing from earliest infancy, showing diffuse osteosclerosis, fractures due to fragility, and change in the blood morphology—anaemia, hemoglobin even down to 20 per cent, micro- and macro-erythrocytes, poikilocytosis, etc. Enlarged posterior clinoids, optic atrophy, and sequestration of the lower mandible may be noted. The blood calcium is usually doubled. No evidence that the parathyroids are involved has ever been offered.

Osteopoikilie—"osteopathia condensans disseminata"—of which 72 cases are on record, recognized by the punctate or linear striation of the bone, often accompanied by scleroderma and dwarfism, is described. Another interesting condition is myositis ossificans progressiva which in 62 to 70 per cent is accompanied by microdactyly.

Of various other conditions described may be mentioned lung atelectasis, perforation of the kidney pelvis and ureter during pyelography without severe clinical symp-

¹⁸*Radiothérapie Gynécologique*. Par R. Mathey-Cornat, radiologiste des hôpitaux. etc. 265 pages. Masson et Cie, Paris, 1936.

¹⁹*Ergebnisse der Medizinischen Strahlenforschung*. Herausgegeben von Holfelder, Holthausen, Juengling, Martius und Schinz. Band VII. 622 Seiten mit 294 Abbildungen im Text. Verlag von Georg Thieme, Leipzig, 1936.

In the operation for fibroids he counsels the retention of the cervix unless special indications for complete hysterectomy are found. Unlike so many German authors, he does not approve of re-infusion of the blood shed into the peritoneal cavity in ectopic gestation but prefers a donor for the transfusion.

In the treatment of tuberculosis of the adnexa he favors small, frequently repeated dosage of x-ray. In unilateral ovarian malignancy, he advises bilateral oophorectomy and hysterectomy unless the indications for limiting the procedure are very strong.

In the operation for tubal ligation, he describes the inguinal canal route in utmost detail with 19 illustrations. There are also numerous operations described for the treatment of malpositions of the uterus. In the treatment of cystocele, although the technique includes careful separation and elevation of the bladder, a modified Stoltz circular suture is still employed. He likewise exposes the levators and sutures them together in perineorrhaphy.

Although one may differ in minor details and have preferences for modification of technique, it is a pleasure to read this book and to study its excellent illustrations.

—R. T. Frank

The purpose of this small work, *Urology in Women*,¹⁵ is to present only the urologic lesions peculiar to women. The incompleteness necessitated by such an intention rather limits the usefulness of the book by making it an adjunct to larger works on surgery or urology.

In revising the text an interesting discussion of the rather rare lesion of endometriosis of the bladder has been included, as well as a section on vesical neck obstruction. Among the notable revisions are the discussion of changes in the ureters during pregnancy and menstruation, the dietary treatment of pyelitis and on nephroptosis. There is a marked tendency to recommend proprietary therapeutic agents by their trade names.

The subject matter is well handled and the book should be useful, though in no sense a work of reference.

—Philip F. Williams

*The Results of Ovarian Grafting*¹⁶ is a report presented by Mocquet and Cotte before the Forty-fifth Congress of the French Surgical Association. The subject of this monograph is divided into 2 main parts, the first dealing with experimental grafts by Mocquet, the second and larger portion with surgical grafts in the human being by Cotte.

This short monograph will be found of great use for anyone interested in finding the literature and the results obtained in ovarian grafting. The conclusion that homographs and heterographs are rarely of value is in keeping with the general experience of the profession.

—R. T. Frank

Schubert in a small monograph¹⁷ describes the technic of his operation for the establishment of an artificial vagina. His material comprises 32 patients operated upon, with one death. The operation, beautifully illustrated, utilizes the lower portion of the rectum for the artificial vagina. Then, through the sacral route, the upper portion of the rectum and sigmoid are drawn down and sutured, within the anal sphincter, to the skin.

¹⁵*Urology in Women*. By E. Catherine Lewis, M.S. (Lond.), F. R. C. S. (Engl.). Surgeon to Royal Free Hospital, etc. Second edition. Illustrated, 100 pages. William Wood & Company, Baltimore, 1936.

¹⁶*Résultats des Greffes Ovariennes*. Pierre Mocquet de Paris et Gaston Cotte de Lyon. 126 pages. Association française de Chirurgie, XLV Congrès française de Chirurgie, Paris, 1936.

¹⁷*Die Künstliche Scheidenbildung aus dem Mastdarm*. Von Dr. Gotthard Schubert. 69 Seiten mit 35, teils farbigen Abbildungen. Ferdinand Enke Verlag, Stuttgart, 1936.

The second portion of this short monograph is a description of causes of leucorrhea and its treatment. Little new has been added to our knowledge for the relief of this unpleasant symptom.

—R. T. Frank

*Facts and Frauds in Woman's Hygiene*²⁴ by Rachel Palmer and Sarah K. Greenberg is a medical guide for the laity against misleading claims and dangerous products. It is well written, terse, and hits straight from the shoulder. There is no hesitation in mentioning innumerable products which have gained a large number of users simply through misleading advertising. In addition, the various subjects discussed should give the reader additional insight. The entire realm of "feminine hygiene" including menstruation, dysmenorrhea, irregularities, leucorrhea, sterility, and contraceptives is taken up. Certain particularly dangerous drugs such as those containing amidopyrine are singled out. The book should fulfill a want for those who are in doubt about many of these subjects, among whom I am loath to confess many physicians must be included.

—R. T. Frank

Sex Problems

Havelock Ellis has written a *Psychology of Sex*²⁵ as a manual for students. In this comparatively short volume of 377 pages, he has compressed the contents of his seven preceding treatises. As heretofore he emphasizes the normal phenomena of sex and shows how wide a frontier exists between the normal and the abnormal.

The statement that in scientific knowledge of sex, physicians are often less informed than their patients, must be conceded as true. He describes the biology of sex, including its determination by the chromosome, the intersexual form, hormonal deviations in later life, the sex impulse itself, the erogenous zones, and the periodicity of sex impulse, furthermore, the relation of the 5 senses to sexual impulses.

He next takes up children, particularly libido as a general manifestation. In children there can be no homosexuality where there is not as yet a conception of sexuality. The discussion includes such well-known matters as the Oedipus complex, masturbation, narcissism, etc., in detail. The sexual impulse in youth and sexual deviations in the adult are described and analyzed. Among the main contents of the book are chapters on marriage and the art of love.

This very sane treatise which does not attempt to enter into the subject of psychoanalysis, although it does not deny its applicability in appropriate cases, is not only of extreme value to the student, but should be in the library of physicians as well.

—R. T. Frank

*The Single Woman and Her Emotional Problems*²⁶ is a sympathetic study of the psychologic difficulties of the large group of more or less independent single women who are forced to live out their lives as best they can without the natural fulfillment of their normal physiologic functions. To this group of women with sympathy and an evident understanding the book is offered.

The author discusses the origin of this group of women which she feels results from the further education of women, their professional training and in part the aftermath of the dislocation of society following the World War. She discusses the

²⁴*Facts and Frauds in Woman's Hygiene*. By Rachel Lynn Palmer and Sarah K. Greenberg, M.D. 311 pages. The Vanguard Press, New York, 1936.

²⁵*Psychology of Sex. A Manual for Students*. By Havelock Ellis. 377 pages. Emerson Books, Inc., New York, 1935.

²⁶*The Single Woman and Her Emotional Problems*. By Laura Hutton, Physician. Institute of Medical Psychology, London. William Wood & Co., Baltimore, 1935.

toms, and tuberculous adnexitis in which 80 per cent are cured by x-ray therapy. On the other hand, in nonmalignant uterine bleeding radium is preferred to roentgen rays.

The last 3 papers deal respectively with the treatment of esophageal carcinoma, lymphogranulomatosis, and radiotherapy in the treatment of mammary carcinoma. The reproductions of the x-ray photographs which play a large rôle in the description are extremely good.

—R. T. Frank

The second edition of *Gynecology for Nurses*²⁰ by the Drs. Crossen is a well-planned, attractively prepared book. It is well designed for study and teaching, profusely illustrated, and covers the subject in a very readable fashion because of its precision and directness.

Particular attention has been paid in this new edition to our most recently acquired knowledge of physiology, especially to that of the ovary and the pituitary. There is a very clear chapter on endocrine disorders.

—R. T. Frank

*Prostitution*²¹ by Tage Kemp is based on investigations made in Copenhagen, partly financed by the corporation of the city and partly by the Rockefeller Foundation. The text deals with the abolition of the regulations of prostitution in Denmark, as well as with the laws now in effect. The very evident fact that only 29.4 per cent of those examined were mentally normal and without defective intelligence is emphasized. This is a serious contribution to the subject.

—R. T. Frank

The second edition of Kahr's *Conservative Therapy of Women's Diseases*²² follows the first after an interval of only two years. The author has covered the field very fully in such a fashion that either the general practitioner or the specialist can readily find all the current methods applicable to a given condition. In this new edition such advances in hormonal therapy as have been developed in the last few years have been incorporated. In the treatment of infantile gonorrhea, just as in this country, exhibition of large doses of estrogenic substance is advocated. For the cure of gonorrhea, however, I see no mention of hyperthermia, a new method which is being used in this country with increasing frequency and good results. As so often is the case in books of this type, a huge number of prescriptions are incorporated in the text.

—R. T. Frank

The second enlarged edition of Hans Runge's monograph on *Bleeding and Leucorrhœa*²³ appears as Volume IX of *Medizinische Praxis*, a series for post-graduate education of physicians.

The second edition takes full cognizance of the changes in our knowledge of functional bleeding based on hormonal investigations.

²⁰*Gynecology for Nurses.* By Harry Sturgeon Crossen, Professor Emeritus of Clinical Gynecology, Washington University School of Medicine, etc., and Robert James Crossen, Instructor in Clinical Gynecology and Obstetrics, Washington University School of Medicine, etc. Second edition, with 357 engravings including one color plate, and 316 pages. The C. V. Mosby Co., St. Louis, 1936.

²¹*Prostitution.* By Tage Kemp, M.D., Copenhagen. Translated from the Danish by Elsie Marie Werner Kørnerup. 253 pages. Levin & Munksgaard, Copenhagen, 1936.

²²*Konservative Therapie der Frauenkrankheiten.* Von Professor Dr. Heinrich Kahr, Vorstand der I. Universitäts-Frauenklinik in Wien, etc. Zweite, neubearbeitete und vermehrte Auflage. 327 Seiten. Verlag von Julius Springer, Wien, 1937.

²³*Blutung und Fluor.* Von Professor Dr. Hans Runge, Direktor der Universitäts-frauenklinik, Heidelberg. Zweite, erweiterte Auflage, mit 18 Abbildungen auf 117 Seiten. Verlag von Theodor Steinkopf, Dresden, 1936.

This discussion of *Contraception as a Therapeutic Measure*²⁸ concerns the 1,152 dispensary patients referred to the Bureau for contraceptive advice in Baltimore by physicians. Since this survey was conducted in a southern city it is somewhat surprising that only one out of five patients was colored. In any study of the use of contraceptives it is generally believed that the patient must be intelligent enough to understand a rather exact technic, and it is interesting to note that Dr. Moses considers that 60 per cent of her patients had a low degree of intelligence and only 4 per cent had a high degree of intelligence. She states that contraceptives had been used previously by many of her patients before they had been referred to the Bureau and only 15 per cent had any success in their attempts to limit their families.

A noteworthy fact brought out by the study of this group of women shows that there has been a very high abortion rate; approximately 37 per cent of the 981 nontherapeutic abortions were admitted to be either criminally or self-induced, and the average number of abortions per patients had been 2.1 per cent.

In a group of women advised as to methods recommended, namely, the vaginal diaphragm, vaginal jelly, and douche, only 2.1 per cent of the total treated patients were actual failures, and in a group who became pregnant, a gross number of 234, roughly 71 per cent, were women of low intelligence. In the women who became pregnant, either the method advised had not been used or ineffective material or faulty technic seemed to be responsible factors. Over 22 per cent of the patients treated could not be located for follow-up work. A noteworthy finding was the physical and mental improvement observed in many women due to the respite from childbearing and relief from fear of pregnancy. No definite injury or sterility was noted following the use of the method.

This Bureau began with a very definite purpose of studying women in whom physicians felt contraception was advisable and this small book represents the worth while factual presentations of the work done. To those who are interested in the statistical aspect of birth control this book will be of value.

—Philip F. Williams

This *Medical History of the Control of Conception*²⁹ gives a comprehensive review of the age-long and world-wide attempt, for one reason or another, of all peoples to limit reproduction. In such a widely collective study, the social and economic imputations are of almost equal interest with the medical and historical items presented. The book appears under the aegis of the National Committee of Maternal Health, one of whose members, Dr. Dickinson, has written a friendly foreword in which he implies that organized medicine has sidestepped its responsibilities in not taking an active part in the discussion of this vital problem of control of conception.

The material is divided in six parts. Contraceptive technique before the dawn of written history discusses the known or traditional practices of preliterate societies. It is evident that while the desire was wide the practice of contraception was narrow, and the population was limited, if not by disease then by abortion, infanticide, or sexual taboos. Through antiquity, Egyptian papyri, the ancient Jewish books, and the writings of the early Greeks and Romans the discussion of the problem in its various aspects is traced. Among the available sources of early eastern cultures the tenuous thread is followed in China, Japan, and India, and pursued through the manuscripts of the Islamic period of medicine and the folk beliefs and lay literature of the middle ages. It is of passing interest to note that the etymology of the word "condom" has not been solved.

²⁸*Contraception as a Therapeutic Measure.* By Bessie L. Moses, M.D. 90 pages. The Williams & Wilkins Company, Baltimore, 1936.

²⁹*Medical History of Contraception.* By Norman E. Hines, Ph.D. Illustrated, 521 pages. The Williams & Wilkins Company, Baltimore, 1936.

friendships which arise between members of these groups, often sad substitutes for the companionship of marriage, remedies for loneliness, attempts to satisfy maternal instincts and other emotional states. Her handling of the psychologic problems involved gives excellent advice to women who have joined in a friendship unequal in one respect or another.

The author very sanely discusses the sexual problems of the single woman and their relationship to her unfulfilled wifehood and maternity. Her discussion of masturbation and homosexuality is clear and easily understandable by the lay person and should be of great help in the instances where such problems are presented for solution. Sexual inversion and other perversions and neuroses of a similar type, as well as alcoholism and drug addiction are analyzed, not only from the point of origin but as well of treatment.

In concluding the book, the author recapitulates the adjustments which may have to be made by many single women in their relationships to other women. She very wisely denies that the adoption of a child could be considered a suitable remedy for many of the problems of the single woman. She suggests many ways in which sexually unexpended emotional energy may be distributed in numerous and varied interests. This is an excellent book to be read by the single woman herself, by her medical advisor, and by her religious advisor.

—Philip F. Williams

The Married Woman,²⁷ written in collaboration by a well-informed sociologist and a physician, who is also a gynecologist and teacher, comprises a very practical volume for married women, with a clear and sane discussion of the various problems and situations which frequently confront her. The book begins with the physiologic and psychologic attitudes and inhibitions of postpuberty and early maturity period which influence the woman in marrying or not marrying. There follows a consideration of the right attitudes for the woman who is to be married, bringing out an especially important point, namely, the health of the two parties to the marriage and the significance of various diseases in their future intimate union. This chapter forms an excellent basis for the education of the physician who may be consulted for premarital advice. The physical relationship of marriage is described in a succeeding chapter with particular reference to mental as well as physical adjustments in the marriage act. As the book proceeds the problems of the "seasoned wife" and the common problems of marriage such as family relationship, her husband's business interests, her own gainful employment, as well as the marital relationship, are taken up. The advice is practical in every respect.

The subject of motherhood and woman's fitness for motherhood particularly, with regard to the state of her health as well as that of her husband, with a pointed passing reference to induced abortion, makes the subject matter of an excellent chapter. The hygiene and physical changes of pregnancy, the subject of prenatal care and delivery are simply described but with emphasis on necessary points of value. The re-adjustments when the wife becomes a mother is plain common sense. For the married woman who remains sterile, the chapter on the childless wife with its excellent advice as to overcoming the mental frustrations in the completely sterile woman will be of help. The book proceeds with a discussion of the period of age fixation and the time of the menopause and describes the mental and sexual maladjustments and changes which are often present at such times.

This book may be heartily recommended to all women and the reading of it will tend to a more sympathetic understanding by the physician of both the mental and sexual problems which his married patients may bring to him for solution.

—Philip F. Williams

²⁷*The Married Woman*. By Gladys H. Groves and Robert A. Ross, M.D. 278 pages. Publishers: Greenberg, Inc., New York, 1936.

The subjects which will appear in successive issues are of equal historical and immediate interest. I mention only a few: Addison's disease, Banti's disease, Dercum's disease, and Mikulicz's disease.

—R. T. Frank

Dr. Jacoby, who has previously discussed the interrelation of law and medicine, and education and medicine, considers in *Physician, Pastor, and Patient*³⁷ topics of mutual concern to medicine and religion. The openminded presentation of the many subjects should promote a better understanding and cooperation of the two great forces aiming at human betterment.

The first part of the book is devoted to an historic and philosophic reflection upon the development and practice of modern medicine. In the second part of the book, the effect of superstition upon medicine, the relation of various forms of religion to the general problems of hygiene and health are discussed, and chapters on the patient's faith and the inexplicables in medical practice are introduced. The third part of the book deals directly with such vital problems as may be presented to the physician and clergyman simultaneously. As Dr. Jacoby says the relationship is connoted by the cry of the tragedy-stricken home "telephone for the doctor and send for the priest." Here he takes up contraception and artificial abortion, the divorce problem, sterilization, sex education, euthanasia, vivisection and the problem of privileged communications. These sections present a well-thought-out argument, pro and con, to help the medical and religious adviser where such problems arise and their counsel is sought.

This stimulating presentation may be profitably read by both physicians and ministers in order that they may develop a rational meeting ground in their mutual problems.

—Philip F. Williams

*Medicine and Mankind*³⁸ is a series of seven lectures given at the New York Academy of Medicine by prominent physicians for the instruction of the lay public. A wide field is covered. The subjects are such diverse topics as: How We Learned About the Human Body, Medicine in the Days of Louis XIV, Contributions to Medicine of the American Aborigines of Both Continents, Constitutional Factors in Disease, Organic Background of the Mind, Vitamins, and the Mystery of Death. Both the lay public and physicians will find this interesting and instructive reading.

—R. T. Frank

Miscellaneous

*Syphilis and Its Treatment*³⁹ is a timely book. There are many treatises on syphilis but with the present program of the Public Health Services and associated institutions to make a concerted drive to eradicate this needlessly common disease, there is, as the author states in his preface, a need for a clear, simple and relatively complete account of the disease and its treatment. The author has admirably succeeded in this aim.

In reviewing the book for this special journal one may omit the generalities of the topic and examine the portions of the book relating to obstetrics. It is noteworthy that aside from a discussion of the site of the initial lesion in the female,

³⁷*Physician, Pastor, and Patient. Problems in Pastoral Medicine.* By George W. Jacoby, M.D. 390 pages, illustrated. Paul B. Hoeber, Inc., New York, 1936.

³⁸*Medicine and Mankind. Lectures to the Laity delivered at the Academy of Medicine in New York.* Edited by Jago Goldston, M.D. 217 pages. D. Appleton-Century Company, New York, 1936.

³⁹*Syphilis and Its Treatment.* By William A. Hinton, M.D., Boston, Mass. 321 pages. The MacMillan Company, New York, 1936.

After a review of the recent past, the trials, the handbills, and the notoriety period, ending in the story of the career of Margaret Sanger, the author brings one to the best of the book, a philosophical sociological analysis of the present status and technic of birth control with reflections upon the ethnical and political angles and possibilities of this world-wide movement. The documentation of the book is sweeping in its inclusiveness; there are over seventy pages of author and source references.

This book will rank high for years as a reference work in this particular field of medicine and sociology.

—Philip F. Williams

The Single, the Engaged and the Married,³⁰ by Maurice Chideckel, does not strike the right note. It appears to overemphasize sexuality, even for a book of its kind. The physician reader will find it replete with errors. Such a statement as appears on page 37, "fourteen women past thirty-five had each a fibroma, or benign tumor, of the uterus. They had the tumor because they were not married, a high price for not obeying the laws of Nature," is a fair example. The book is unsuited to the lay reader because of the accentuation of sex abnormalities which would prove misleading.

—R. T. Frank

The Physician

No more delightful book³⁵ can be put in the hands of a last year medical student or a young doctor waiting for patients soon after he has started in practice, than this mellow, understanding book written by Wingate M. Johnson. It is entitled *The True Physician* with the subtitle *The Modern "Doctor of the Old School."* It lives fully up to its title. This book is based on lectures to the graduating class of Duke University. Among other things, it contains the principles of ethics of the American Medical Association.

Included in the topics discussed are the interne locating for practice, the modern family doctor, the choice of general practice, specialization, group practice, or public health work.

Most understandingly the author discusses the early days of practice. It is replete with valuable advice. Among other things, he warns against the drug addict and the woman seeking abortion who drift into the doctor's office. The doctor as a citizen, the business side of practice, contacts with law and courts, and even the personal side of his life, contemplated marriage, social relations are taken up. The final chapter discusses what reading young medical men can do, not only medical but cultural. Altogether delightful reading.

—R. T. Frank

Volume I, No. 1 of *Medical Classics*,³⁶ compiled by Emerson Crosby Kelly, contains a short biography and a full bibliography of Sir James Paget. In addition the full text of the three best-known contributions of this famous physician and scientist is given in full with reproduction of the original illustrations. This includes "On a Form of Chronic Inflammation of Bones (Osteitis Deformans)," "Additional Cases of Osteitis Deformans," and "On Disease of the Mammary Areola Preceding Cancer of the Mammary Gland."

This makes accessible in very attractive form these contributions which are now difficult to refer to and which today are as important as when they were published.

³⁰*The Single, the Engaged and the Married*. A treatise on the mutual adjustment for the attainment of happiness in marriage. By Maurice Chideckel, M.D., 268 pages. Eugenic Publishing Co., Inc., 1936.

³⁵*The True Physician. The Modern Doctor of the Old School*. By Wingate M. Johnson, M.D. 157 pages. The MacMillan Co., New York, 1936.

³⁶*Medical Classics*. Compiled by Emerson Crosby Kelly, M.D. Department of Surgery, Albany Medical College. The Williams & Wilkins Co., Baltimore, 1936.

the cervix. No mention of lymphogranuloma inguinale is given, although esthiomène probably covers some of these cases. I am surprised to note that menopause flushes are treated by repeated venesection. Likewise, the injection of glycerin every two hours into a septic abortal uterus does not appeal to me. The same author likewise describes the gynecologic operations which are given in extenso. Sterility in women is dealt with by Forsdike. The major emphasis is placed on the mechanical aspects of sterility. Tumors of the ovary are described by Green-Armytage. This chapter is short and insufficient.

The urinary system and the male genital organs are covered by Ainsworth-Davis. The preliminary investigations and diagnosis are very well dealt with. The ketogenic diet is described in detail but more emphasis is placed on the acidification of the urine by mandelic acid. In the treatment of undescended testes, no mention of preputiary preparations is made.

An interesting chapter on the sympathetic nervous system by A. Lawrence Abel will be found. The anatomy of the abdominal sympathetic is very clear. There is a short but interesting exposition of this new field.

To me the most interesting and original contribution is on the adrenal gland by Broster and Vines. Broster, who describes the surgery, has 15 cases of virilism operated upon without a death, an amazingly good record. Vines offers a new test for determining the presence of the virilism factor in the adrenal by means of a Fuchsinophil stain (Ponceau fuchsin).

The next portion deals with injection treatment of hernia, hemorrhoids, hydrocele and varicocele, and varicose veins.

The concluding chapter by Buxton covers the subject of orthopedics.

Much of interest not only to the general profession but also to surgeons will be found in these pages.

—R. T. Frank

Pineus' *The Eggs of Mammals*⁴¹ is a most interesting and stimulating short monograph. It deals with the behavior of the mammalian egg from its genesis in the ovary to its implantation in the uterus. The author does not believe that the definitive ova of adult life arise from the primordial germ cells. On the contrary, he favors the view that the mammalian ova have a short life with a periodic production of new ova, the rate of their proliferation varying with the various stages of estrus and pregnancy cycles. The determining factor, according to Pineus, is the pituitary secretion which inhibits follicular changes, favoring maturation of the ova.

He considers regeneration of ovogenetic tissue improbable in mammals, based on the work of Parkes, but concedes the regeneration of anovular follicles after x-ray destruction of the existing ova. These anovular follicles are capable of producing ovarian hormones.

While the reviewer realizes that in such pioneer studies some evidence though hypothetical must be considered, he cannot agree with the view expressed that granted that pituitary secretions are concerned with the promotion of ovulation and luteinization they presumably inhibit ovogenesis to a certain extent; nor that the thyroid may promote ovogenesis directly. The facts at present available are far too slender to warrant any definitive judgment. This applies as well to hypothetical atresia suppressing hormone.

This monograph is very well worth reading. It is the first of a series of experimental biology monographs of which 14 others are already announced.

—R. T. Frank

⁴¹*The Eggs of Mammals.* By Gregory Pineus, Assistant Professor of General Physiology, Harvard University. 160 pages, illustrated. The MacMillan Company, New York, 1936.

practically no reference is made to lesions of the disease in the female reproductive tract. The incidence of the disease in pregnant women is discussed from the racial angle. The primary lesion in the cervix is believed to be frequently overlooked or as frequently not recognized. The alcohol test (page 51) is not considered satisfactory in the female. The discussion of the infecting of married women by husbands early in the tertiary stage is of note in explaining the occurrence of syphilis, with no history of lesion or symptoms, in pregnant women.

The chapter on syphilis and marriage brings out clearly and significantly the position of the obstetrician or family physician in preventing social and reproductive tragedies. The advice given is concise and the author's conclusions are clinically sound. The chapter on congenital syphilis shows an estimated percentage of that condition in from 2 to 5 per cent of our population. The ideas of transmission are well established, the rules for preventing congenital syphilis are modern and effective, and the author feels that this proportion of syphilis could be almost entirely prevented. He recommends a routine Wassermann of every pregnant woman regardless of social status. Fortunately, this practice in clinic service is slowly but surely gaining in the United States. There is an excellent discussion of the signs, symptoms, and therapy of congenital syphilis. On page 275 under treatment of syphilis during pregnancy, caution is advised in the dosage of the heavy metals and arsenicals on account of the possibility of injury to the kidneys and liver.

This book should be read by the obstetrician, who in his work has the opportunity to promptly eliminate congenital syphilis, as well as to educate a large portion of the public in the campaign to eradicate the disease.

—Philip F. Williams

The second volume of *Postgraduate Surgery*,⁴⁰ edited by Rodney Maingot, contains more than 1,800 pages. The subjects covered include the head, spinal column, and salivary glands by Wakeley. The treatment of head injuries is very conservatively handled. An interesting chapter on cranial tumors is given. The advice that pituitary adenoma and carcinoma, if unaccompanied by papilledema, may be treated by radiotherapy is given. This entire part is illustrated with excellent x-ray photographs.

The neck is dealt with by Wheeler who uses either local, block, or rectal oil ether anesthesia. Avertin is not mentioned. The parathyroids are discussed very cursorily. No inclusion of scleroderma or Raynaud's disease is found. The breast by Love is much scantier in contrast to other important chapters. Both the anatomy and operative technic are barely touched upon. The important subject of the breast and its diseases deserves much more adequate treatment.

In contrast to this, the thorax is dealt with in considerable detail by two authors, Sleigh Johnson and T. Holmes Sellors. Johnson treats of postoperative chest complications and artificial pneumothorax. He discusses the medical aspects of chest troubles, including lung collapse, embolism, postoperative pneumonias, abscess of the lung for which he advises "bronchoscopic aspiration," cardiovascular complications, artificial pneumothorax. Much apparatus is described and illustrated.

The subject of surgery of the thorax is taken up by Sellors. This includes resection of the ribs for tuberculosis, phrenicectomy, empyema, both acute and chronic, but a description of the operation for pulmonary embolism is not included. The surgery of the chest concludes with tumors and bronchiectasis. This is very good.

The female genitals are described from various aspects. Regional Gynecology and Gynecological Operations are by J. Lyle Cameron. Apparently the watch spring rubber pessary is still used abroad. He emphasizes Schiller's test for carcinoma of

⁴⁰*Postgraduate Surgery*. Edited by Rodney Maingot, Senior Surgeon to the Royal Waterloo Hospital and to the Southend General Hospital, etc. Volume II. With 1,134 figures in the text, 3,572 pages. D. Appleton-Century Company, New York, 1936.

and their balancing, form an interesting story well calculated to be understood and appreciated by the layman. Such dietary aberrancies as vegetarianism and fasting are discussed.

The problem of weight control is simply and clearly explained, and the patent medicine fakes and ballyhooed diets debunked. Three well-constructed diets, for a fortnightly period to lose, maintain or gain weight are detailed. The statement is made that weight loss should at no time exceed two pounds a week. There are included standard 100 calorie tables and percentage element food source graphs. The book may be warmly recommended to the public.

—Philip F. Williams

Dr. Logan Clendening, author of several books on medical subjects written essentially for the laity, now turns to food. His latest is *The Balanced Diet*.⁴⁶ In it the author in his well-known clear, interesting style presents a discussion of the constituents of foods as well as diet in health and disease from a middle-of-the-road point of view. There is also a commendable attack upon food faddism, and here he writes energetically and with malice aforethought.

Regardless of what one's opinion may be as to the propriety or advisability of the dissemination of medical literature to the general public by physicians, it must be admitted that this book will be extremely valuable not only to the laity but also to physicians. Since the written is always so much more efficacious than the spoken word, it may help the latter in perhaps eliminating some of the skepticism that patients not infrequently manifest when certain healthful but obnoxious diets are prescribed.

Numerous tables and illustrations showing the constituents of the common foods as well as their caloric value are also presented.

—Frank Spielman

This widely used dictionary⁴⁷ with the appearance of this new, revised edition celebrates its twenty-fifth anniversary. It reflects the latest revisions of the U. S. Pharmacopocia and the National Formulary with the addition and elimination of many drugs, and changes more recently adopted in chemists' spelling. The elimination of required instruction in Latin and Greek by many American colleges made it desirable to include a short chapter on medical etymology, dealing with medical orthography and the common prefixes and suffixes, Latin and Greek, used in medical nomenclature. There also is added a list of English terms which by the Anatomical Society of Great Britain and Ireland have been suggested to replace in part the official Basle Anatomical Nomenclature.

—Hugo Ehrenfest

*Boy or Girl*⁴⁸ by Dr. Jules Regnault, who according to the title is ex-professor of anatomy at the Naval Medical School, is a farrago of nonsense based particularly on the defunct Albert Abrams' method. Regnault also presided at a conference of "radiotellurists and sorcerers." In his biography, supposedly written by the editors, it mentions that he operated upon himself under local anesthesia for hernia. According to the text, women can have the choice of girls or boys to suit themselves, if they follow the directions given by the author.

—B. T. Frank

⁴⁶*The Balanced Diet*. By Logan Clendening, M.D., Professor of Clinical Medicine, University of Kansas. Illustrated, 267 pages. D. Appleton-Century Co., New York, 1936.

⁴⁷*Medical Dictionary*. By Thomas Lathrop Stedman, A.M., M.D. Thirteenth revised edition. Illustrated, 1,291 pages. William Wood and Company, Baltimore, 1936.

⁴⁸*Yille ou Garçon*. Par Docteur Jules Regnault. Editions Medels, Paris, 1936.

This volume, the seventh in *Les Problèmes D'Oncologie*,⁴² is dedicated to the memory of M. I. Lifshitz. It is written in Russian but, fortunately for the reviewer, a majority of articles have summaries in French and English. While the English is somewhat quaint, it is understandable.

The 19 articles are by numerous authors. One group deals with gastritis and its relation to carcinoma. Another group describes the effect of "prolan" upon the growth of experimental cancer. The final group concerns itself with clinical cancer, including that of the skin which appears to be extremely prevalent on exposed parts in the Ukrain. Radiotherapeutic measures for combating clinical cancer are discussed.

—R. T. Frank

Volume I, Part 2, of *The Patient and the Weather*,⁴³ contains 781 pages, with innumerable graphs, maps and illustrations. The first volume was devoted to the graphic distribution of diseases in the United States, with the inference that meteorologic environment had much to do with the reaction of the human organism. According to the author, medicine has concentrated too much on infectious diseases. He quotes Haldane as saying that we must direct our views from microorganisms to the patient. This will imply closer study of the environment. The constitution of the patient should take into consideration the limitations of biological reactions as regulated by the autonomic nervous system and as influenced by the meteorological environment, in normal individuals to start with, including chemical, endocrine and nervous factors. The organism swings in a definite rhythm, increasing and decreasing as far as its oxidation, its pH, metabolism, blood pressure, etc., are concerned. The peaks and drops are both of clinical significance. Even the possible changes of the human organism in response to the ordinary common meteorological changes have been studied. A wealth of clinical detail and statistics are included. This book will appeal to the statistically minded because of the huge amount of data and documentation.

—R. T. Frank

Cobb's *Preface to Nervous Disease*⁴⁴ is based on fourteen years' teaching of second-year students in neuropathology. To quote the author's own words, it is "a brief, concurrent anatomy, physiology, and pathology." In a short compass of 173 pages, this large task is attained by means of careful selection and compression. Simple but well-executed diagrams as well as a short bibliography at the end of each chapter add to the value of this manual.

—R. T. Frank

*Food, Fitness and Figure*⁴⁵ is a story of our sources of strength and health written for the intelligent public. The subject is one of universal interest, and the facts presented are not only correct but are given in a very pleasing manner. The structure of the dietary elements, their basic components, the sources and need for iodine, calcium, the vitamins and the beverages, the constituents of a normal diet

⁴²*Les Problèmes D'Oncologie*. Tome VII. Édition Médicale d'État D'Ukraine, 1935. (In Russian.)

⁴³*The Patient and the Weather*. By William F. Peterson, M.D. Volume I, Part 2. Automatic Integration. Illustrated, 781 pages. Edwards Brothers, Inc., Ann Arbor, Mich., 1936.

⁴⁴*A Preface to Nervous Disease*. By Stanley Cobb, M.D., Bullard Professor of Neuropathology, Harvard Medical School, etc. 173 pages. William Wood & Company, Baltimore, 1936.

⁴⁵*Food, Fitness and Figure*. By Jacob Buckstein, M.D., Consulting Physician in Diseases of Stomach and Intestines, United States Veteran Bureau, etc. 252 pages. Emerson Books, Inc., New York City, 1936.

microscopic diagnosis of cervical cancer will not be improved until both the clinician and the pathologist learn more about pseudomalignant and possible premalignant lesions of the cervix.

Mitotic figures are occasionally seen in the basal layer of the normal cervical epithelium and are to be looked upon as evidence of the normal growth and repair of the cervix.

Cervical lesions may be spoken of as "precancerous" when it is understood that the term implies that they might, though not necessarily will, become cancerous.

Leucoplakia of the cervix is a pathologic entity which may show cellular changes suggestive of cancer, though invasion is always lacking.

An interesting case is described of intracervical carcinoma, diagnosed with the aid of the Schiller test, and in which the malignant growth extended over the entire endometrial surface of the uterus.

The importance of biopsy is indisputable, but its value is increased if the specimen is immediately fixed and serial sections are made.

The application of Lugol's solution with the atomizer simplifies the Schiller test which is undoubtedly of some value in the diagnosis of early cancer; whether it is a specific test for the absence of cancer is questionable.

WM. C. HENSKE.

Wetterdal, P.: Does the Microscopic Diagnosis Afford a Prognostic Guide in Cervical Cancer? *Acta obst. et gynec. Scandinav.* 14: 302, 1934.

In the Radium Home at Stockholm a study was made of 354 cases of cervical cancer to determine the relationship between the histologic appearance of the cancer and the results obtained with radium treatment. Clinically the cases were divided into the four groups proposed by the Cancer Commission of the League of Nations and the cases were followed for at least five years. The percentage of cures for the different groups was so nearly identical that the author believes it safe to assume that the microscopic appearance of the cancer is of no prognostic significance. Kamniker came to the same conclusion from an analysis of cases studied microscopically and treated either by operation alone or by combined operation and radiation therapy.

J. P. GREENHILL.

Feldwig: The Relation Between the Histology, the Prognosis, and the Therapy of Genital Carcinoma, *Ztschr. f. Geburtsh. u. Gynäk.* 111: 1, 1935.

Feldwig studied 422 cases of cancer of the uterus, vagina, and vulva histologically. He divided the cases into four grades: ripe, middle ripe, unripe and structureless. He found adenocarcinoma and squamous cell cancer present in the same lesion in 2.1 per cent of all the cases. The ratio of squamous cancer to adenocarcinoma of the cervix was about 10 to 1; and the same ratio, but reversed, applies to cancer of the fundus of the uterus. He found that the maturity of the cancer cell increases with the age of the patient. There are differences in radiosensitivity in the various grades of cancer, but an absolute radioresistance does not exist. Adenocarcinoma of the cervix was found to be more resistant to radiation than was squamous cancer. Fractional irradiation produces the best results in cancers of the middle ripe group regardless of location or cell differentiation. A moderate number of mitoses and a moderate degree of hornification as well as a cellular reaction (lymphocytes, leucocytes or eosinophiles) indicate the most favorable prognosis from irradiation. Surgical results were slightly better in the cases of low maturity than those with more advanced maturity. (The reviewer does not believe that the author's figures for adenocarcinoma-squamous cancer ratio

Department of Reviews and Abstracts

CONDUCTED BY HUGO EHRENFEST, M.D.

Selected Abstracts

Carcinoma

Reimers, Carl: Results With the Klein Carcinoma Reaction, München. med. Wehnschr. 83: 1375, 1936.

Reimers reports on the Klein reaction in 691 blood tests made on as many patients. Of these, 438 cases were definitely diagnosed clinically and histologically as follows: (a) 38 cases of malignant tumors (not skin carcinomata) with the Klein reaction positive in 32 and negative in 6, a correct average in 84.3 per cent; (b) 28 cases of benign tumors giving a positive Klein in 2 cases and negative in 26 cases, a correct average in 92.9 per cent; (c) 372 cases that were cancer-free with a positive Klein in 19 cases and a negative reaction in 353 cases, a correct average in 95 per cent. Among the 691 cases there were also 24 which had not been completely studied when the Klein reaction was made, but in which finally the reaction was determined to be correct in 23 instances and false in 1, a correct average of 96 per cent. There were also 172 cases in which certain factors, such as preceding x-ray and radium treatments, operations, medications, hemorrhages, etc., might be considered as interfering with the proper interpretation of the Klein reaction, a fact to which Klein himself has called attention. Of these 172 cases there were (a) 42 cases with malignant tumors in which the results were correct in 33.4 per cent and false in 66.6 per cent; (b) 130 cases which included those that had benign tumors and also those that were tumor-free in which the results were correct in 70 per cent and false in 30 per cent. The remaining 57 cases were not available for complete and final diagnoses. Although the percentage of correct results was slightly higher in the nonmalignant cases, the malignant conditions seemingly can be diagnosed with a certainty in about 90 per cent of cases.

C. E. PROSHEK.

Grögler, Fritz: Experience With the Klein Carcinoma Reaction, München. med. Wehnschr. 83: 1377, 1936.

Grögler summarizes his results with the Klein carcinoma reaction in 90 clinic cases, suspected of having malignant tumors. There were available for exact study 68 cases in whom there were no disturbing or complicating factors. In 92.6 per cent of these the Klein reaction proved to be correct. This corresponds with the findings of other clinics.

C. E. PROSHEK.

Hendriksen, Erle: Precancerous and Carcinoid Lesions of the Cervix Uteri With Comments on the Schiller Test, Surg. Gynec. Obst. 60: 635, 1935.

In the great majority of cases, the diagnosis of carcinoma is simple, either clinically or pathologically, and microscopic examination is only confirmatory. The

demonstrating this point. To what extent the various experimental factors such as trauma, estrin, and corporin, respectively, are responsible for the results obtained also needs further analysis.

WM. C. HENSKE.

Crossen, R. J., and Hobbs, J. E.: Relationship of Late Menstruation to Carcinoma of the Corpus Uteri, *J. Missouri M. A.* 32: 361, 1935.

The incidence of late menopause in cases of adenocarcinoma of the fundus uteri is about four times as high as it is in normal cases. In this series, a study of the slides of previous curettages done in fundal carcinoma cases indicates that endometrial hyperplasia is an important predisposing factor in adenocarcinoma of the fundus. A study of such slides whenever possible will help to settle definitely the question of the importance of endometrial hyperplasia as an etiologic factor in fundal cancer. Late menopause, especially when extending to the age of fifty, is a warning of a tendency to endometrial malignancy, and adequate treatment should be given to stop the aberrant endometrial activity.

J. THORNWELL WITHERSPOON.

Wittenbourg and Zlatmann: Post-Climacteric Hemorrhages and Their Relation to Malignant Neoplasms, *Rev. franç. de gynéc. et d'obst.* 30: 1026, 1935.

The authors collected 100 personal cases of postclimacteric bleeding among which 41 per cent had malignant growths causing the bleeding. They collected from literature 2,384 reports of postclimacteric bleeding. In this series the incidence of malignancy was 62.8 per cent. Other causes were benign neoplasms in 4.5 per cent, inflammatory disease in 20.3 per cent, urinary tract affliction in 0.6 per cent, diverse causes in 6.9 per cent, and unknown causes in 4.9 per cent.

Some gynecologists objecting to exploratory curettement, in cases of postclimacteric bleeding perform a hysterectomy on the clinical symptoms alone. The present authors are not of this opinion because otherwise they would have performed unnecessary operations on a large proportion of their patients. Since most of these women are old and in poor physical condition, there is a high operative mortality for hysterectomies.

J. P. GREENHILL.

Henriksen, Erle: Carcinoma of the Cervix Uteri, *Arch. Surg.* 31: 461, 1935.

From a clinical study of 940 cases of cervical cancer the author draws conclusions among which the following seem noteworthy: The average age of these patients was forty-six years, with cancer occurring in 66.3 per cent before the age of fifty years. Over 10 per cent were never pregnant. Postcoital spotting occurred in less than 5 per cent. In 50 per cent there was some involvement of the urinary tract, mostly nocturia. Loss of weight or pain has no diagnostic value. The possible influence of heredity is still a disputed question. Among the 940 cases were 22 in which the cancer developed in a cervical stump after subtotal hysterectomy with an average lapse of five years.

HUGO EHRENFEST.

Ulrich, P.: Cancer of the Cervix. The Etiologic Rôle of Previous Surgical Traumatism, *Compt. rend. Soc. franç. de gynéc.* 6: 238, 1936.

In the opinion of the author it is an established fact that the traumatism of labor plays an important rôle in the etiology of cancer of the cervix. However, this form of injury does not exist as a forerunner of cervical carcinoma in nullip-

in the fundus of the uterus can be accepted, nor that his statements on the comparative radiosensitivity of adenocarcinoma could be substantiated by workers in this country.)

EUGENE S. AUER.

Norris, Charles C.: Adenocarcinoma of the Cervix, *Am. J. Cancer* 27: 653, 1936.

A compilation of 9,505 cases of cervical cancer reported in literature shows an incidence of 5.7 per cent for adenocarcinoma of the cervix, a relatively small percentage. Analyzing 43 cases seen in the gynecologic service of the Hospital of the University of Pennsylvania, Norris arrives among others at the following conclusions: Adenocarcinoma of the cervix presents many different histologic types. It seems that the embryonal (unripe) tumors are about twice as fatal as the ripe or adenoma malignum neoplasms. In general the proportion of cells undergoing mitosis offers a fairly accurate guide as to the degree of malignancy and radiosensitivity. Adenocarcinomas are more prone to develop in the cervical canal and in this situation the first symptoms appear later which means it often is rather far advanced when diagnosed. As a group they are not less sensitive to irradiation than the epitheliomas of the same region.

HUGO EHRENFEST.

Overholser, Milton D., and Allen, Edgar: Atypical Growth Induced in Cervical Epithelium of the Monkey by Prolonged Injections of Ovarian Hormone Combined With Chronic Trauma, *Surg. Gynec. Obst.* 60: 129, 1935.

The ovarian follicular hormone has been shown by Allen and many others to be a powerful stimulator of epithelial growth in the female genital tract and breast.

Atypical epithelial growth in the cervix uteri of 4 ovariectomized monkeys (Monkeys 1 to 4) was experimentally produced. The changes consisted of marked squamous epithelial downgrowth, overgrowth, and epidermization of the cervical glands in the region of the junction of the stratified squamous with the columnar epithelium. The treatment these animals received was as follows:

Monkey 1 received 5,490 R.U. of estrin in ninety days, with repeated cervical trauma.

Monkey 2 received 1,660 R.U. of estrin in twenty days, with repeated cervical trauma.

Monkey 3 received 4,747.5 R.U. of estrin and 14 c.c. of corpus luteum extract in 81 days with repeated cervical trauma.

Monkey 4 received 2,802.5 R.U. of estrin and 10.7 c.c. of corpus luteum extract in eighty-four days. This animal did not receive cervical trauma and the changes were very pronounced, the epithelial cells being very atypical.

In three other monkeys the results were practically negative possibly due to the following reasons: (1) injection period too short (Monkey 5); (2) sloughing of epithelium from severe infection (Monkey 6); (3) sloughing of epithelium from infection and from stopping hormone injections forty-two days before sacrificing animal. (Monkey 7.)

A normal control (Monkey 8) receiving trauma only showed a slight amount of epidermization of cervical glands.

An ovariectomized control (Monkey 9) receiving trauma only was completely negative.

It should be possible by repeating these experiments and extending them over much longer periods of time to determine experimentally whether the changes in question will or will not develop into cancer in the monkey. Either result would be highly important and experiments are now being carried out with a view to

prevention. Because of the large incidence of cervical cancer following subtotal hysterectomy in multiparas, the author reserves this operation for single women only.

F. L. ADAIR AND S. A. PEARL.

Reckmann, R.: *Sarcoma of the Cervical Stump*, *Arch. f. Gynäk.* 155: 478, 1936.

The author reports the occurrence of a spindle-cell sarcoma in a cervical stump. A necrotic submucous fibroid the size of a fetal head had been removed together with the uterus by means of a supravaginal hysterectomy, and seven months later a necrotic tumor of the cervix as large as the primary tumor of the uterus was found in the cervical stump and protruding into the vagina. This was removed and the patient was given intensive irradiation in spite of the fact that the tumor resembled benign fibromyoma when examined microscopically. Six weeks later there was a fist-sized recurrence which was found to be a typical spindle-cell sarcoma. The author is of the opinion that the primary tumor was sarcomatous as well.

RALPH A. REIS.

Fahndrich, Joachim: *The Risk of Carcinoma of the Cervix Following Supravaginal Hysterectomy*, *Ztschr. f. Geburtsh. u. Gynäk.* 109: 382, 1934.

The author reports 12 cases of cervical stump cancer treated in the Kiel clinic between 1922 and 1933. A fairly complete compilation of the world statistics concerning stump cancer and its relation to supravaginal hysterectomy is presented. Several theories about the etiology of this type of cancer are mentioned, mostly discarded as probably erroneous. The only definite factor is that the condition is seen far oftener in the multipara than in the primipara or virgin. The author believes that cancer may develop at any time after the original operation, but the first year is the most dangerous. The incidence of cervical stump cancer in the Kiel clinic was 0.28 per cent when compared with the number of supravaginal operations done; the figure is 0.39 per cent in the accumulated statistics of literature. Regardless of prophylactic precautions such as coring out the cervical canal, or cauterization with the actual cautery or phenol, or the careful discrimination in choosing patients for this operation, a certain small percentage of cancers will develop in the stump. At first glance this would tend to make the argument in favor of the complete removal of the uterus and cervix overwhelming. However, the author then makes an extensive study of the mortality figures in the various large clinics of the world, comparing the figures for the complete operation with those of the supravaginal operation, and finds that in uncomplicated cases there is a minimum difference of 1.75 per cent in favor of the supravaginal operation. This figure increases materially in the face of complications of more extended operations. It therefore follows that even if all the patients developing stump cancer would die from that disease, the mortality of the supravaginal hysterectomy would still be materially less than the mortality from abdominal total extirpation of the uterus.

EUGENE S. AUER.

Séjournet, P.: *Cancer of the Cervix After Subtotal Hysterectomy*, *Bull. soc. d'obst. et de gynéc.* 24: 278, 1935.

The author reports two cases of cancer of the cervix after subtotal hysterectomy. In a study of the literature he found a total of 387 cases published up to 1935. Up to 1926 there were reports of only 85 such cases but from 1926 to 1935, 302 additional cases have been added. The author obtained his statistics from two

arous women. In these cases, the author believes, mechanical damage inflicted by surgical instruments is an important factor. Especially dangerous are the Museux forceps which have damaging prongs with which the cervix is grasped. The sharp pointed teeth of this clamp carry healthy epithelium into the depths of the cervix and here under certain conditions the cells become transformed into cancer. Because of this, the author has had constructed a special form of this instrument which he believes cannot injure the cervix.

J. P. GREENHILL.

Döderlein, G.: Cancer of the Cervix in Young Women, *Ztschr. f. Geburtsh. u. Gynäk.* 110: 349, 1935.

In the author's clinic 48 women under thirty years of age were found with cancer of the cervix, i.e., 5.15 per cent of all cervical cancer cases seen. In 44 of the 48 cases a period of but four months or less had elapsed since the onset of the first symptoms. The operability rate was 92 per cent, an unusually high figure for any series of cancer cases. The 48 cases were treated as follows: 41 with Wertheim operation; 2 with Wertheim operation preceded by radiation; 1 with Schauta operation; 4 with radiation therapy only. There was a total five-year cure rate of 48 per cent (absolute), and a five-year cure rate of 52.3 per cent in the operable cases. Döderlein concludes from a study of these cases that there is no reason for the prevalent pessimism in the prognosis of the disease in young women, if the diagnosis is made at the proper time and proper therapeutic measures are instituted. There is no difference in the response of younger patients to operation, radiation or a combination of the two, than in the older woman. The results should be about the same, if not better, in the younger woman because her physical condition, as a rule, will be better. He believes that every young woman treated by a radical operation should have a transplantation of a healthy ovary into the rectus sheath.

EUGENE S. AUER.

Tompkins, Pendleton: Statistical Study of the Relation of Parity to Carcinoma of the Cervix Uteri, *Am. J. Cancer* 25: 624, 1935.

It is doubtful whether the relation between parity and cervical cancer can be reliably determined from the statistics at present available. However, from computations based upon such data as could be secured, it appears that in the United States in 1930, among women thirty years of age or over, the death rate from cervical carcinoma was at least twice as great among those who had borne children as among those who had not.

HUGO EHRENFEST.

Stout, T. D. M.: Cancer of the Cervix Uteri, *New Zealand M. J.* 34: 97, 1935.

Conditions arising in the cervix following parturition and their relationship to cancer are discussed. Two generally accepted precursors of cancer are trauma and sepsis. Erosion and chronic cervicitis, in view of their prolonged infective nature and chronicity, are opposed as causative factors by some and held responsible by others as possible precursors of cancer.

The author concludes from various records that trauma alone is not responsible for the development of cancer. The weight of evidence points to the theory of cancer's being due to chronic infective processes. Leucoplakia is definitely a pre-cancerous lesion.

Early diagnosis and prevention are discussed in detail. Biopsy is advocated for diagnosis and treatment of chronic infections of the cervix as a means of

Carcinoma of the uterine corpus is usually of the glandular type. Diagnosis can generally be made by a curettage but cancer should be suspected in patients who commence to have a discharge or bleeding after the menopause. Carcinoma of the body is best treated by a course of deep x-ray therapy followed promptly by a panhysterectomy.

J. THORNWELL WITHERSPOON.

Malpas, P.: Corporeal Recurrence After Radium Treatment of Carcinoma Cervicis, Lancet 2: 1464, 1935.

There were 5 cases in 359 cervical carcinomas that had corporeal recurrences after radium therapy. The symptoms of the recurrences were irregular lower abdominal and lumbar pain and a return of the watery discharge. The uterus enlarged and became globular. Extension to the ureters and bowel are common complications. It is emphasized that hysterectomy has no place in the secondary treatment of cervical carcinoma for at least twelve months after radium treatment and that the uterine applicator be sufficiently long for treatment.

H. CLOSE HESSELTINE.

Mackenzie, Kenneth: Advanced Cancer of the Cervix Treated With Acetone and X-Radiation, New Zealand M. J. 35: 309, 1936.

Two cases of squamous cell epithelioma of the cervix in an advanced stage were treated by the application of pure acetone followed by x-ray irradiation. A marked improvement in the symptoms occurred immediately following this treatment and ultimately the ulcerating lesions which filled the vaginal vault completely disappeared. One year later both patients appeared free from the disease.

One other case treated similarly by the author resulted in only temporary alleviation of the discharge.

F. L. ADAIR AND S. A. PEARL.

Mackenzie, Bruce: Radiotherapy of Cancer of the Cervix Uteri, New Zealand M. J. 34: 171, 1935.

Radiologic treatment of cancer involves a distinction between two factors: alleviation or cure. Alleviation is obtained upon incomplete eradication of cancer cells. This applies to advanced, widespread, hopeless cases. Cure comprises complete eradication of all malignant cells and their conversion into benign tissue. The author deals with this group particularly.

Fundamentally, an adequate dose to all cancer cells and a regulated dose that will cause no damage to normal surrounding tissues are essentials.

There is no fixed lethal cancer dose. Some radiosensitive cancers may be eradicated by a dose of 1,000 r., while radioresistant types may not be cured by 10,000 r. Between these extremes lie many gradations. The percentage of cures increases with increasing dosage. Damage to normal tissues must be avoided. Normal tissue tolerance varies with different tissues. In gynecologic work 3,000 to 4,000 r. tissue dose may be safely given in the course of a month. A homogeneous distribution of dosage through the entire tumor area is essential. X-ray may be used beneficially in conjunction with radium. Methods of x-ray treatment and their sequelae and complications are described. Local reactions, diarrhea, cystitis, vaginitis, and amenorrhea with sterility commonly follow, and all but the last require treatment.

sources, namely, Surgical Services and Anti-Cancer Clinics. The cases covered by the Surgical Services were small in number compared with the large series reported by the Anti-cancer Clinics. From large series of cases reported by surgeons the incidence of cancer of the cervix after hysterectomy was 2.19 per cent, whereas in the series reported by cancer clinics the incidence of late cervical cancer was 4.17 per cent. The author collected 9 instances of cancer which developed in the vaginal scar. He discusses the treatment of late cancer of the cervix.

J. P. GREENHILL.

Barthélemy: Cancerization of Fibroids, *Bull. Soc. d'obst. et de gynéc.* 25: 164, 1936.

The author points out that three signs indicate a cancerous change in a fibroid. These are in the order of their frequency: pain, a foul discharge, and emaciation. The pain is continuous, in the pelvic region, with attacks of exacerbation and radiation to the lumbar region and the thighs. The vaginal discharge is liquid, thin and foul smelling. A woman who has uterine fibroids may be anemic and weak from loss of blood, but she does not become emaciated. However, when the fibroid becomes cancerous, the woman becomes cachectic.

The author collected from the literature 34 cases of fibroids which underwent cancerous change. In this collected series 23 complained of pain, 14 mentioned that they had a foul discharge and 9 showed emaciation.

It is important to make a diagnosis of cancerous change of a fibroid because if radiation therapy is employed without this knowledge, the favorable time for a total hysterectomy has passed. This is essential because this operation is the only rational treatment for cancerous change of a fibroid.

J. P. GREENHILL.

Fournier, R.: Cancer of the Body of the Uterus After Irradiation for Metrorrhagia, *Bull. Soc. d'obst. et de gynéc.* 24: 309, 1935.

The author reports a case where cancer occurred in the body of the uterus after the patient had received x-ray therapy for metrorrhagia. In the literature, particularly German, he found 65 cases of uterine cancer after radiotherapy for benign gynecologic conditions. The interval of time between radiation and appearance of the cancer varied from two months to ten years. The author does not believe there is any justification to admit a causal relationship either direct or indirect. An irradiated uterus is not predisposed to cancerous changes.

In half of the published cases it was doubtful whether the original condition for which the radiation therapy was used actually was benign. It is more probable that the cancer existed before the treatment with x-rays. The author emphasizes that in every case of uterine bleeding before radiotherapy is used a curettement should be performed, and all material examined microscopically. In some cases intrauterine injection of lipiodol may be used or a biopsy of the cervix made.

J. P. GREENHILL.

Dickinson, Arthur M.: Modern Treatment of Carcinoma of Uterus, *Am. J. Surg.* 32: 395, 1936.

Carcinoma of the uterine cervix is usually of the epidermoid type. Accurate histologic diagnosis by biopsy is essential; biopsy risk is very slight. Cervical carcinoma is best treated by a combination radium and deep x-ray therapy. By the use of the deep therapy before radium application the danger of fatal peritonitis is minimized. Surgical treatment has proved inadequate in comparison with radiotherapy.

Auer, E. S.: *Carcinoma of the Cervix*, J. Missouri M. A. 32: 47, 1935.

Auer analyzes 136 cases of cancer of the cervix treated at a St. Louis Cancer Hospital from January, 1927, to January, 1930. Twenty-nine or 21.3 per cent were cured. A complete follow-up was obtained on all patients. The cervical malignancies were grouped according to the classification of the American College of Surgeons.

Auer believes that the radical operation, either by vaginal or abdominal route, has a very definite place in the treatment of cervical cancer, provided its use be reserved for those patients in whom there is absolutely no extension of the disease laterally. Radiation, combined with conservative surgery, is the method of choice in borderline cases. A watchful waiting policy should never be adopted in suspicious cervical lesions. Radium treatment of this disease should be carried out only by those who are qualified.

J. THORNWELL WITHERSPOON.

Greenhill, J. P., and Schmitz, Herbert: *Intraspinal (Subarachnoid) Injections of Alcohol for Pain Associated With Malignant Conditions of the Female Genitalia*, J. A. M. A. 105: 406, 1936.

Twenty-seven subarachnoid injections of alcohol in 25 women suffering excruciating and persistent pain from advanced carcinoma of the genitalia were made. Relief lasting from two weeks to six months was attained in 24 out of 25 patients. For 21 of the injections 0.5 c.c. of 95 per cent alcohol was used and injected into the fourth lumbar interspace. The technic varies only slightly from that of the lumbar puncture and is surely much simpler than any operative procedure such as sympathectomy which the writers had recommended for the same purpose two years ago.

GROVER LIESE.

Organotherapy

Neumann, H. O.: *Treatment With Female Sex Hormones*, Med. Klin. 32: 79, 1936.

The author treated many women with female sex hormones for a number of different gynecologic ailments. The results in cases of primary amenorrhea were not satisfactory. In secondary amenorrhea the author obtained encouraging results with a combination of estrogenic hormones and progestin. The patients felt much better physically and mentally. However, in the prolonged cases of secondary amenorrhea, the results were not satisfactory. In many cases with weak and infrequent menstrual periods, favorable results were obtained with estrogenic substance. In cases of hypoplasia of the uterus there was a growth of both the body of the uterus and the endometrium. In seven cases of dysmenorrhea the pain was relieved by follicular hormones. Treatment in these cases had to be continued at least six months. Likewise benefit was observed in women with severe menopausal symptoms. The author was also able to help some women with ulcerations in the vagina and vulva and pruritus vulvae. Using corpus luteum hormone he was able to bring to a successful issue two cases of habitual abortion.

J. P. GREENHILL.

Westman, A.: *Hormonal Therapy for Menstrual Disturbances and the Theoretic Reasons for It*, Acta obst. et gynec. Scandinav. 15: 233, 1935.

In the Upsala Clinic, a number of women with menstrual disturbances were treated with various hormones. In two out of three cases of primary amenorrhea, favorable results were obtained with prolan and estrogenic substance. In 17 cases

The author feels that where no reactions occurred an inadequate dose was administered. The larger doses, though drastic, give the best results. Early treatment is most important from the radiologic aspect because (1) the area involved is smaller, and (2) young tumor cells are more vulnerable than old ones.

F. L. ADAIR AND S. A. PEARL.

Carranza, Felipe F.: *A Consideration of the Treatment of Carcinoma of the Vulva*, *Boll. de Soc. de ostet. y ginec. (Buenos Aires)* 15: 369, 1936.

After reviewing his cases and results obtained by the several methods employed the author arrives at the following conclusions:

The treatment of choice in carcinoma of the vulva is electrosurgery not only of the local area, but also of the areas of regional metastasis, and extirpation of the lymph glands, four to six weeks following the vulvectomy. During the interval deep x-ray therapy is applied over these areas.

The technique of treatment varies with the extent of involvement. Simple vulvectomy suffices in very early cases. In them, if the initial lesion is small, radium may be employed. In lesions of the second and third grade electrosurgery with electrocoagulation of all regional lymph glands must be employed.

It is best not to close the denuded areas with sutures but permit them to granulate.

MARIO A. CASTALLO.

Salacz, Paul von: *The Surgical Treatment of Cancer of the Female Genitalia*, *Ztschr. f. Geburtsh. u. Gynäk.* 110: 290, 1935.

Operable cancer of the cervix is best treated by a combination of radiation and radical surgery which gives 18 per cent better results than either method alone. In the II. University Clinic of Budapest the radical vaginal operation (Schauta) is used rather than the abdominal operation of Wertheim because the final results are about the same, while the primary mortality, postoperative morbidity and complications are much greater with the abdominal operation. Inoperable cancer, as well as operable cancer complicated by old age, diabetes, hyperthyroidism, cardiorenal disease, etc., is treated only by radiation. Over a period of seventeen years, 217 cases of cervical cancer were operated by the Schauta method. Primary mortality was 3.6 per cent and morbidity 7.7 per cent. Uneventful recovery without a rise in temperature occurred in 55 per cent. There were 46.5 per cent of five-year cures. Pregnancy complicated by cancer of the cervix does not have the extremely bad prognosis generally believed. Cancer in pregnancy is treated by radical methods, either with or without cesarean section, depending upon the period of gestation and the extent of the cancer at the time that it is discovered. In his clinic the results were about the same as with cancer not complicated by pregnancy. Cancer of the uterine body is best treated by vaginal hysterectomy. The five-year cure rate in 81 cases was 73 per cent. Cancer of the vulva was treated by radiation, although the author describes the correct surgical procedure. No end-results are greater, but the prognosis is given as very bad. A few cases of cancer of the vagina were treated surgically with the results extremely unsatisfactory. Two cases of primary cancer of the tubes were seen. The patients lived less than one year after operation. Three cases of Krukenberg tumor are reported. Regardless of the age of the patients all ovarian tumors should be operated as soon as possible. Of 130 cases operated more than five years ago 36.9 per cent are living and well. Inoperable cancers of the ovaries are treated by radiation, but the results are universally bad.

EUGENE S. AUER.

Scanty menstruation with dysmenorrhea is benefited by progynon intramuscularly or orally during the first half of the interval. Menopausal symptoms respond favorably to progynon treatment orally in mild doses and by injection twice a week in severe cases. The indiscriminate use of hormones should be avoided.

F. L. ADAIR AND S. A. PEARL.

Vogt, E.: The Treatment of Undernutrition and Secondary Amenorrhea by Implantation of the Hypophysis of a Newborn and With Estrogenic and Luteal Hormones, *Med. Klin.* 31: 1393, 1935.

The author had under his care a thirty-three-year-old woman who exhibited severe undernutrition associated with a secondary amenorrhea. The latter had existed for sixteen years and had begun at the time of a severe attack of the grip. All known methods of therapy were tried without any beneficial effects on the patient's weight or her amenorrhea. Finally the author implanted the pituitary gland of a newborn infant into the musculature of the abdominal wall. Excellent results followed. The patient began to gain weight immediately and at the time of the report had gained 31 pounds. After the gain in weight started, the long-standing amenorrhea was treated with estrogenic and corpus luteum hormones and then menstruation took place. The patient received a total of 1,700,000 international units of estrogenic substance in six injections and 180 units of progesterin in 7 injections. Bleeding took place thirty days after the beginning of the treatment.

J. P. GREENHILL.

Goldberg, M. B., and Lisser, H.: Clinical Use of Emmenin, *Endocrinology* 19: 649, 1935.

Emmenin-Collip, an alcohol soluble, ether insoluble complex present in acetone extracts of human placenta was given an adequate trial in 100 instances of various menstrual disorders, occurring in 66 women. It has proved helpful in restoring menstruation if periods have been absent less than a year. It is probably useless in amenorrhea of longer duration. In eight of nine cases of oligomenorrhea (delayed periods) the menstrual interval was more nearly regularized. The same result was accomplished in seven patients whose menstrual interval was utterly irregular, sometimes too soon, other times too late. Polymenorrhea (consistently too frequent periods) was unaffected by Emmenin (only 3 cases). Hypomenorrhea (scanty flow) was definitely improved in nine of twelve cases. Menopausal symptoms and cyclic menstrual headaches were relieved in a fair majority of cases. In two of four cases of sterility pregnancy occurred under Emmenin therapy. Over 60 per cent of 40 subjects with severe dysmenorrhea were remarkably relieved. Psychic factors were rigidly excluded. This constitutes its most significant clinical usefulness. Emmenin deserves a place in the therapeutics of menstrual disorders. The chief objection, at present, to its widespread use in clinical practice, is its expense.

J. THORNWELL WITHERSPOON.

Zondek, B.: Gonadotropic Stimulation Therapy, *Acta obst. et gynec. Scandinav.* 15: 1, 1935.

Until the present time hormone therapy has been purely substitutional. Zondek believes that in the future hormone therapy should be one of stimulation. He indicates that hormones should be administered in order to stimulate the glands which produce hormones. He emphasizes that prolan is a gonadotropic hormone

of secondary amenorrhea the following results were observed: No success in three cases treated with prolan. One good result in 4 treated with estrogenic substance given hypodermically. Among 5 cases of secondary amenorrhea, treated by a combination of prolan and estrogenic substance, there were 2 successes and 3 failures. In 3 cases of puberty bleeding, prolan produced considerable improvement in one cases and partial help in two other instances. Among 8 women with menopausal bleeding treated with corpus luteum hormone only 3 showed good results. For climacteric disturbances, estrogenic substance administered by mouth proved helpful.

J. P. GREENHILL.

Fairlie, Margaret: Ovarian and Pituitary Hormones, Brit. M. J. 2: 533, 1935.

A hypoplastic uterus may be induced to grow and develop to normal size by estrin. During pregnancy estrin and the mechanical stimulus of the placenta ensure progressive growth of the uterus. The estrin level in the blood rises from time of rupture of follicle until menstruation, which is accompanied by a sudden drop. In the urine estrin is excreted during the normal menstrual cycle in amounts from 1,200 to 2,000 M.U. During pregnancy it is excreted in amounts over 50,000 M.U. in twenty-four hours. It has been suggested that the placenta produces a large part of it during pregnancy.

Progestin acts on the uterine endometrium only after it has been sensitized by estrin. If pregnancy occurs, progestin is responsible for the formation of the decidua, and the arrest of the ripening of fresh follicles. The periodicity and rhythm prevailing in uterus and ovary throughout normal sexual life are obviously under the control of the anterior pituitary gland.

In castrated animals, castration cells appear in the anterior pituitary; these may disappear on the administration of estrin and reappear on withdrawal. Thus the interrelationship of the pituitary and ovary are observed, i.e., the anterior pituitary stimulates the production of estrin, and the estrin affects the anterior lobe.

The question is yet unanswered as to what is responsible for the rupture of the graafian follicle and ovulation. It is claimed that there is a sudden rise in prolan A in the urine in the mid-menstrual cycle, which may be the stimulus to ovulation.

Metropathia hemorrhagica is an entity characterized by amenorrhea of some weeks' duration, followed by hemorrhage lasting for weeks. It is associated with multiple follicular cysts and represents an anovular menstruation. No corpus luteum is present. The endometrium is hyperplastic, containing dilated, cystic glands, and areas of necrosis in the superficial layers of the membrane. Estrin is credited as the source of the marked hyperplasia of the endometrium during the period of amenorrhea. Administration of estrin is, therefore, contraindicated in this form of uterine bleeding. Curettage is advisable for diagnosis and the removal of thickened endometrium gives relief in some cases. Corpus luteum hormone (prolution) is giving encouraging results. Resection of the cystic ovary is advisable before resorting to hysterectomy in young people. Patients over 40 can be safely treated by intrauterine application of radium.

In epimenorrhea the treatment is the same. It is a speeding-up of the cycle most common after parturition and attributed to the activity of the anterior lobe persisting. In younger patients, rest, curettage and iron to combat anemia are satisfactory, with hysterectomy as a last resort. In older patients radiation following curettage is most satisfactory.

The knowledge of menstruation without ovulation has offered a new cause for sterility. Examination of the endometrium one or two days before the period is due is, therefore, essential when investigating such an individual.

intensified the symptoms. The exact relationship of the hyperprolanism to the migraine is unknown; however, migraine associated with ovarian deficiency lends itself to a rational control with estrogenic therapy.

J. THORNWELL WITHERSPOON.

Mazer, Meranze, and Israel: Evaluation of the Constitutional Effects of Large Doses of Estrogenic Principle, *J. A. M. A.* 105: 257, 1935.

From a survey of the literature and the clinical study of 30 patients, it was found that injections of from 100,000 to 200,000 rat units of estrogenic substance, given in divided doses over periods of from two to three months, produce no appreciable changes in body weight, basal metabolism, blood pressure, blood count, coagulation and bleeding times, blood chemistry and urine.

In 6 of 17 regularly menstruating women, injections of these large quantities of estrogenic substance produced a temporary delay in the menstrual flow (from one to three weeks) and established in these six patients a new date of onset of the menses. This phenomenon is apparently due to a temporary inhibition of the anterior pituitary lobe.

Growth of the mammary glands and increased libido were observed in a few of the treated patients.

Relatively larger doses of the estrogenic substance (from 85,000 to 150,000 rat units) than those employed clinically produced neither macro- nor microscopic changes in the vital organs of 30 rabbits. The response of the ovaries to huge doses of the estrogenic substance is either degenerative or stimulative, depending on the species and age of the test animals and the duration of administration of the substance.

GROVER LIESE.

Joachimovits, R.: Contribution to the Treatment of Uterine Bleeding in the Preclimacterium, *Wien. klin. Wchnschr.* 49: 365, 1936.

In a study of 150 uteruses removed at operation from women during the preclimacteric years, the author made the following observations: There were senile changes in the uterine muscle; there was protoplasmic shrinking of the basal layers of the endometrium; hyalinization and atrophy of the uterine mucosa. On the basis of these histologic findings involving both the endometrium and the myometrium the author made injections of follicular hormone in experimental animals. He reasoned that just as the endometrium has its cycle, the myometrium likewise has its cycle. Injection of follicular hormone into experimental animals produced a myoblastosis in the uterus. If the cause of preclimacteric bleeding is muscular in origin, the injection of sex hormone to produce myoblastic islands in the uterine wall is rational. A better treatment consists in a combination of follicle hormone plus sekalin, the latter having a direct effect on the muscular wall also. In 30 cases he found this combination to give satisfactory results.

W. B. SERBIN.

Schaefer, R. L.: Menopausal Hypertension, *Endocrinology* 19: 705, 1935.

In the series of 13 subjects of menopausal hypertension there occurred a substantial reduction of the hypertension and amelioration of all the associated symptoms after the administration of theelin. The data secured indicate that hypertension frequently develops during the menopause and there is an evident incretory imbalance present at that time. It appears that there is an actual lack of a follicular hormone (theelin) and that its replacement is logically indicated.

J. THORNWELL WITHERSPOON.

the effect of which can be further strengthened by a synergistic factor. This synergistic factor Zondek calls "Synprolan." For the combination of prolan and synprolan the name "Prosylan" is recommended. The anterior pituitary lobe produces and stores prolan and synprolan, whereas the urine of pregnancy contains only prolan. Zondek has definitely shown that in man as well as in animals prolan alone has a distinct gonadotropic action. It was the ability to excite into action an ovary which previously did not function, to stimulate an already functioning ovary to increased activity, and to reawaken the function of an ovary which had previously ceased to function. In a case of a twenty-two-year-old girl with primary amenorrhea and a hypoplastic uterus, Zondek was able to produce typical ovarian function by administering 15,000 rat units of prolan.

J. P. GREENHILL.

Witherspoon, J. Thornwell: The Endocrinal Origin of Primary Dysmenorrhoea and Its Hormonal Treatment, *Endocrinology* 19: 403, 1935.

The most recent explanation of primary dysmenorrhea is an endocrine imbalance. The pain of primary dysmenorrhea can be explained by the withdrawal of the progestin influence, which results in whipping into marked activity, by the action of the follicular hormone, a uterus which has been lying in a quiescent state for ten days to two weeks.

The rationale of treatment in this condition is to counterbalance the follicular hormone activity by administering the luteinizing principle found in the urine of pregnant women. The method of treatment employed was to inject intramuscularly and daily, from three to four days previous to the expected flow, and one to two days during the flow, 250 R.U. (1 c.c.) of follutein. Thirteen of seventeen patients so treated for dysmenorrhea experienced relief.

J. THORNWELL WITHERSPOON.

Hofstätter, R.: Organo Therapeutic Researches on Pineal Extract With Special Reference to Sexual Excitability, *Wien. klin. Wchnschr.* 49: 136, 1936.

The mechanism of the pineal gland is still not understood. Pineal extract has been assumed to produce a depressing effect on sexual irritability not so much by direct action on the ovary, but rather by depressing the sex centers of the mid-brain or higher cerebral centers. There may be an antagonism between the anterior lobe of the hypophysis and the epiphysis. This author over a period of twenty-two years has used an extract of pineal gland in a series of 290 cases. His subjects varied in age from five years to the climacterium and also included patients who were castrated or who had hysterectomy without castration. So far as producing a depressing effect on cases with hyperlibido, his results are variable and inconclusive. Further clinical and experimental work is necessary before definite conclusions can be given.

W. B. SERBIN.

Glass, S. J.: Migraine and Ovarian Deficiency, *Endocrinology* 20: 333, 1936.

A study was made of the prolan A and estrin relationships in 10 young migrainous women with ovarian dysfunction. Quantitative hormone essays showed a reversal of the normal ratio in the direction of increased prolan A and decreased estrin output. Estrogenic therapy tended to correct the hormonal imbalance by suppression of the prolan A secretion with concomitant relief of the migraine symptoms in 80 per cent of the cases. Prolan administration either gave no relief or

Items

American Board of Obstetrics and Gynecology

The next written examination and review of case histories of Group B applicants by the American Board of Obstetrics and Gynecology will be held in various cities in the United States and Canada on Saturday, November 6, 1937.

The next general examination for all candidates (Groups A and B) will be held in San Francisco, Cal., on June 13 and 14, 1938, immediately prior to the American Medical Association meeting.

Application blanks and booklets of information may be obtained from Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh (6), Pennsylvania. Applications for these examinations must be filed in the Secretary's office not later than sixty days prior to the scheduled dates of examination.

American Board of Obstetrics and Gynecology

Diplomates Certified by the American Board of Obstetrics and Gynecology, Inc., June 7 and 8, 1937, Atlantic City, N. J.

The following names are to be added to the list published in the July, 1937 issue of this JOURNAL.

PAUL A. GEMPEL, Kansas City, Mo.

S. LEON ISRAEL, Philadelphia, Pa.

CONSTANTINE J. NICHOLAS, Santa Barbara, Calif.

VICTOR G. H. WALLACE, Toronto, Canada.

Advisory Board for Medical Specialties

The annual meeting of the Advisory Board for Medical Specialties, which is the coordinating Board of the twelve certifying boards in the various specialties, the Association of Medical Colleges, the American Hospital Association, the Federation of State Medical Boards of the U. S. A., and the National Board of Medical Examiners was held at Atlantic City, N. J., on June 6, 1937.

The following officers were elected:

Officers and Executive Committee

Willard C. Rappleye, M.D., *President*, New York, N. Y.

W. P. Wherry, M.D., *Vice-President*, Omaha, Neb.

Paul Titus, M.D., *Secretary-Treasurer*, Pittsburgh, Pa.

W. B. Lancaster, M.D., Boston, Mass.

R. C. Buerki, M.D., Madison, Wis.

Dr. Louis B. Wilson of Rochester, Minn., the retiring president of the Board, was elected an emeritus member of the Board.

Bishop, P. M. F.: The "Pregnancy" Test in Relation to Death of the Ovum, *Lancet* 2: 364, 1935.

The author reports the results of the Friedman test for death of the ovum in 11 cases. The test tends to become negative between the tenth and twenty-fourth days after intrauterine death.

When an intrauterine death is suspected a negative pregnancy reaction will confirm the suspicion but a positive reaction may be present for three months after the fetus has died. Estrin reaction becomes negative considerably sooner than the Aschheim-Zondek and Friedman tests. Yet the former may remain positive for three weeks.

The author was unable to present any additional data on factors which regulate the secretion of gonadotropic hormones by the placenta.

H. CLOSE HESSELTINE.

Campbell, K. C.: A Method for Ovarian Transplantation on Rabbits Used for the Aschheim-Zondek Test for Pregnancy, *J. Lab. & Clin. Med.* 20: 520, 1935.

To avoid repeated posterior or anterior laparotomies on injected rabbits a modified technic of the original Goodale and Flanagan method of ovarian transplantation is proposed. The advantages are: (1) the ovaries are readily accessible; (2) less time is required for the examination as there is only one incision to be made; (3) anesthesia is of short duration and resulting anesthetic deaths are reduced to a minimum; (4) the mortality from infection is greatly diminished; (5) the ovaries are more likely to maintain a normal appearance than is the case if the organs are handled during each examination. The procedure consists of an initial posterior laparotomy, transplantation of the ovaries into the subcutaneous areolar tissue of the back, and subsequent examination by opening the original incision and lifting the skin flaps for inspection of the ovaries. The modification permits repeated examinations after an adequate time for the ovaries to return to normal after a positive reaction. Numerous protocols are cited indicating the value of the method. Vaseline gauze has been discontinued and the incidence of infection further reduced.

W. B. SERBIN.

Witherspoon, J. Thornwell, and Collins, Conrad G.: The Etiology of Functional Puberty Bleeding and the Treatment by Hormonal Therapy, *New Orleans M. & S. J.* 88: 205, 1935.

Idiopathic uterine bleeding results from a hyperplastic condition of the uterine mucosa, which in turn results from ovarian dysfunction. The ovarian dysfunction results from the presence and persistence of multiple follicle cysts in the ovaries. The actual cause of the bleeding in endometrial hyperplasia is probably due to the withdrawal of estrogenic stimulation similar to that which determines the onset of the menstrual flow. The treatment of functional bleedings of puberty, after determining by bimanual examination that no pelvic pathology exists, is as follows: the daily administration of 1 c.c. of follutein, alone or in combination with 2 c.c. of the anterior pituitary growth factor, until bleeding ceases. With the onset of the next flow daily injections are again given until the flow stops. In like manner treatment is carried through a third period. No treatment is given during the fourth period in the hope that the menstrual rhythm has reestablished itself. There is a tendency to spontaneous readjustment of the functional uterine bleeding in young girls. In consequence some of the acclaimed cures might have been spontaneous cures.

EUGENE S. AUER.

in nearly all cases but the impossibility of its beginning during pregnancy is not agreed to by other writers. Courtney believed that pregnancy decreased the rate of growth of the cancer. Later evidence has disproved this. Kermauner insists that proof of the absence of cancer before pregnancy, in cases in which it is found during pregnancy or the puerperium, can only be had by histologic examination of tissue from the cervix taken before the beginning of pregnancy. To this it may be replied that even biopsy is not invariably infallible. We may safely say, however, that only a very small cancer in an advanced pregnancy would permit the assumption that the carcinoma began during pregnancy.

Nearly all pregnant women who have cancer of the cervix are pluriparas. Sarwey remarks that it is rare in a second pregnancy but very exceptional in a first. He could find but seven cases in primiparas. Of 19 cases in the report of Peham and Amreich one only was a primi-gravida. The others had had from 3 to 16 children. Our experience seems to vary somewhat from that of many writers as one of our patients was a gravida ii and the other three were gravidas iii.

Frequency.—In a recent extensive study by Tagliaferro, the incidence of carcinoma in pregnancy was found to be 0.038 per cent. This was based upon figures gathered from a number of clinics. Sarwey has collected the following figures, to which has been added the figure from our own service.

TABLE I

V. Winkel	10 in 20,000
Stratz	7 in 17,832
Glockner	17 in 26,000
Sarwey	2 in 2,287
Danforth	3 in 20,444

In our own work we have found 3 cases of cancer of the cervix in pregnant women. To these may be added one other case, that of a woman who was delivered at another hospital and who came to us for treatment of carcinoma shortly after. Cancer of the cervix was discovered after labor and had certainly been present during pregnancy. A comparison of the percentage of frequency is found in Table II. Our own incidence is calculated upon the three cases which originated in our service, without including one which was admitted subsequent to labor.

TABLE II

Sarwey (combined figures)	0.06 per cent
Williams	0.056 per cent
Tagliaferro (combined figures)	0.038 per cent
Peham and Amreich	0.0302 per cent
DeLee	0.005 per cent
Danforth	0.0144 per cent

Average

0.0321 per cent

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CARCINOMA OF THE CERVIX DURING PREGNANCY*

W. C. DANFORTH, B.S., M.D., F.A.C.S., EVANSTON, ILL.

(From the Department of Obstetrics and Gynecology of Northwestern University Medical School and of the Evanston Hospital)

ALTHOUGH carcinoma of the cervix is found rarely in pregnant women, we have encountered four such cases. If, in a service of moderate size, four cases are seen, it seems essential to have a clear-cut plan for their management. While the incidence of carcinoma in pregnant women varies in the reports of various writers upon the subject, all agree that it is uncommon. This is partly due to the fact that at the age at which cancer is most common pregnancy is less frequent and, conversely, at the age at which most pregnancies occur, cancer is not often seen. Mauriceau believed that pregnancy was impossible in the presence of carcinoma of the cervix. Wertheim suggests that chemical changes in the cervical secretions may render pregnancy less likely. The presence of a large, necrotic carcinomatous crater upon the cervix renders pregnancy quite unlikely. Obstruction of the cervical canal by masses of tumor tissue may also render pregnancy impossible. Cohnstein believed that the likelihood of pregnancy was increased by the presence of carcinoma, but this has long since been demonstrated to be untrue.

It is highly probable that the overwhelming majority of cancers which are found in pregnant uteri were present before the pregnancy began. Kermauner believed that cancer could not begin during pregnancy and that it always existed before pregnancy began. This is probably true

*Read before the Chicago Gynecological Society, November 20, 1936.

NOTE: The Editor accepts no responsibility for the views and statements of authors as published in their "Original Communications."

quency. The reason for this is not apparent. Rarely, rupture of the uterus may occur when extensive carcinomatous invasion has taken place.

Effect of Carcinoma upon Labor.—A small growth, localized upon one lip of the cervix, may cause no obstruction to labor. This was true in one of our cases, although rapid growth occurred afterward. The situation is quite different with large growths. A large tumor mass may obstruct the advance of the head. A carcinoma completely encircling the cervix or invading a large part of its circumference may render dilatation impossible. On the other hand, if a considerable part of the cervical circumference is free from cancer, sufficient thinning and dilatation of the uninvaded portion may take place to permit the infant to pass. Inertia uteri, which may come on after labor has been in progress for a time, may stop labor, the pregnancy then continuing indefinitely.

In some cases in which spontaneous delivery occurs there may be severe injury to the diseased portion of the cervix. Deep lacerations may be caused by the advancing head and these may be followed by severe hemorrhage. Later results are sepsis, thrombosis, or embolism. An extensive carcinomatous invasion is prone to be accompanied by infection, especially if areas of necrosis are present. Dangerous sepsis in the puerperium is especially to be feared.

The pressure of the fetal head and body upon the cancer crushes it and perhaps causes more or less solution of continuity in its tissue mass. This sets free malignant cells and at the same time opens up lymphatic and blood channels. Cancer cells may be forced through the blood and lymph vessels by the trauma of labor into areas not yet invaded. Our observation of extremely rapid progress of cancer growth after labor is in accord with that of a number of writers.

The four cases which we have seen are here briefly reported.

CASE 1.—(No. 50798.) Patient aged thirty-five years, para ii, May 2, 1925. Pregnant five months. Cervix twice normal size, hard, friable, bled easily. The uterus was of the size of a four to five months' pregnancy. Section of a bit of tissue removed for diagnosis was described by the pathologist as follows: "Sections of cervix disclose infiltrating island masses and strands of typical tubular epithelium with many mitotic figures in the nuclei. Sections of the endometrium disclose a similar structure." (J. L. Williams.)

The uterus was emptied on May 9, 1925, by abdominal hysterotomy, the intention being to irradiate as soon as possible after this operation. The operation was followed by infection and peritonitis, death occurring May 20.

CASE 2.—(No. 84500. Dr. C. E. Galloway.) A woman of thirty-seven years was admitted to the hospital July 24, 1930. Two normal labors at term. One pregnancy ended at eight months because of placenta previa. One pregnancy terminated at six months because of toxemia. Menstruation began at the age of fourteen, twenty-eight-day type, lasted four days. Last menstruation June 28.

The cervix was large, long, and was deeply lacerated upon the left side. At the base of the healed laceration was a small lesion, which, upon biopsy, proved to be carcinoma.

The average incidence of carcinoma of the cervix in pregnancy, as shown in these reports, including our own, was 0.0321 per cent. The incidence of pregnancy in women who have carcinoma of the cervix is much greater. This is quite easily understood as pregnancy is a far more frequent and widely spread condition than cancer and one woman may have a number of pregnancies. The frequency in a number of clinics is shown in Table III.

TABLE III

Weibel	1.0 per cent
Katz	1.18 per cent
Williams	1.57 per cent
Glockner	1.79 per cent
Tagliaferro	1.4 per cent

Influence of Pregnancy on Carcinoma.—Some few writers, as Varnier, have believed that carcinoma was not hastened in its growth but actually hindered. This is known at present to be untrue. The rate of growth is influenced by the greatly increased blood supply of the pregnant uterus and by the histologic character of the tumor itself. As in nonpregnant women, some tumors grow faster than others.

During the puerperium, a cancer, which during pregnancy was small, may grow rapidly. In cases in which delivery *per vias naturales* is still possible, rapid spreading of the tumor may be seen after delivery. This is because of the trauma of labor, the advancing head crushing the carcinomatous tissue, opening lymphatics and blood vessels and forcing malignant cells into areas previously uninvaded. This explains the rapid extension of cancer soon after delivery, a fact which is illustrated by one of the cases here reported. The laceration of the diseased cervix caused by labor, with the consequent opening up of lymphatics and blood vessels, predisposes to sepsis, hemorrhage, thrombosis, and embolism. Even though delivery may take place without operative intervention, labor still is gravely dangerous to the mother. In one of the cases included in this report, a lesion which was quite small during pregnancy grew rapidly after delivery and death followed in a few months.

Effect of Carcinoma upon Pregnancy.—A small carcinoma, especially when confined to the visible portion of the cervix, may cause no trouble and may not disturb the normal progress of the pregnancy. As in nonpregnant women, there may be no symptoms.

Abortion is more frequent in the presence of carcinoma of the cervix and is more likely to occur when the cancer invades the cervical canal. The higher the invasion goes the more likely abortion is to occur. Kiwisch believed that abortion or premature labor always occurred when carcinoma was present. Experience has long since shown that he was wrong.

Occasionally pregnancy may proceed without interruption in the presence of extensive cancer. Placenta previa occurs with greater fre-

partly because of the change in size, color and consistency of the uterus. Small blood losses may be looked upon by the patient as threatened abortion and a watery discharge may be confused with the increased vaginal discharge common in pregnancy. On the other hand, the woman who suspects pregnancy often comes to the physician early. The extremely conservative management of abortion which is advocated today may cause the physician to overlook an early cancer. An area of induration in the cervix should raise at once the suspicion of carcinoma. This may be more easily detected because of the soft surrounding cervical tissue. This point has been remarked upon by Tagliaferro, Sarwey and Bar. In our three patients who were seen during pregnancy, the contrast between the hard indurated carcinomatous cervix and the soft normal pregnant cervix was striking. The importance of early diagnosis is so great that, should the character of the lesion be not at once apparent, biopsy should be done. This has been recommended by Sarwey and a number of writers since his work appeared including Tagliaferro. This may be done by a punch forceps or by the electrically heated loop. If the latter is used, the risk of spreading cancer is negligible. If the former is used, the area from which the tissue is taken may be touched with formalin. In any case the danger of harming the woman is slight and not to be considered in view of the paramount importance of timely diagnosis. Advanced carcinoma, presenting cauliflower-like masses, extensive induration, or perhaps a necrotic crater, presents little diagnostic difficulty.

During labor, if the cancer has not been discovered earlier, its presence may be suspected when labor does not progress and a thick, indurated and rigid cervix is found. Advanced carcinoma has been confused with placenta previa, the spongy masses being taken for placental tissue. Such cases have been reported by V. Franqué, Pestalozza, Kermanner, and others. The history here is important. The occurrence of previous moderate bleedings caused by slight disturbance, coitus, defecation, the bleedings occurring at intervals over a considerable part of the pregnancy, speaks for cancer.

The hemorrhage caused by placenta previa is much more profuse. It is entirely independent of trauma and may occur when the woman is completely quiet. The palpatory findings aid in differentiation. In placenta previa the cervix is normal and the placenta may be recognized in the lower uterine segment. The head is held at a higher level by the placental mass. If cancer is present the characteristic carcinomatous induration should be detected by the examining finger in the cervix and cervical canal. If extensive cancerous involvement is present the masses of malignant tissue should be easily recognized.

Cases have been reported (Floel, Hofmeyer) in which cancer and placenta previa have been found together. In such cases the diagnostic

On July 25, as it was thought that an early pregnancy might be present, curettage was done preceding the use of radium. A very small product of conception was obtained. Irradiation was then carried out, 3,500 mg. hours being given. Radium was introduced into the cervical canal, screened by 1 mm. of brass and rubber, and a palisade of needles each containing 10 mg. was placed about the periphery of the growth. An uneventful recovery followed. This woman is still alive and free from demonstrable recurrence.

CASE 3.—(No. 103877.) Patient aged twenty-three, January 7, 1934. This case was seen through the courtesy of Dr. L. W. Mason. Four months earlier she had had her second child, the labor passing without incident. Four years before she had a lesion upon the cervix which was regarded as syphilitic and at that time had a four-plus Wassermann. Prolonged antisiphilitic treatment caused the disappearance of the Wassermann reaction. A one-plus positive Wassermann returned during pregnancy and remained after delivery. The child was normal and cord blood gave no Wassermann reaction. At delivery her physician noted a very small ulcer upon the cervix. Bleeding began early in the puerperium and continued at intervals.

When seen by me a large growth was found which involved the whole cervix. It bled easily upon touching and had all of the palpatory characteristics of cancer. Microscopically a highly anaplastic type of epidermoid cancer was found. On January 10 the accessible portion of the cancer was electrocoagulated. This was followed at once by 3,500 mg. hours of radium, the radium being applied within the cervix and in needles about the periphery. The result was unsatisfactory and death followed on Oct. 10, 1934.

CASE 4.—(No. 116162.) Patient aged thirty-six years, December 28, 1935. Seen through the courtesy of Dr. George Turnbull. Her second pregnancy had reached four months. The first terminated at seven months. Last menstruation August 17. For three months she had had irregular bleeding and had feared she might miscarry. The uterus was enlarged to the size of a four months' pregnancy. Aschheim-Zondek was positive. The cervix was enlarged, indurated, bled easily when touched. Two polyps were visible at the external os. A small bit of tissue was obtained by means of a punch forceps. This was examined by Dr. F. D. Gunn, who reported as follows: "Squamous cell carcinoma of the cervix showing predominance of cells of the basal type and a high degree of anaplasia in some areas." (Grade III.)

As the tumor had broken down but little and the invaded area appeared far cleaner than is the case with most cancers it was decided to risk preliminary emptying of the uterus. This was done on December 20, a short incision being made at the fundus, as far as possible away from the cancerous area. An uneventful recovery followed and upon December 28 the accessible part of the cancer was electrocoagulated. Irradiation immediately followed, 5,000 mg. hours, being given by means of the Curie colpostat, 50 mg. of radium being also placed in the cervical canal screened in 1 mm. of aluminum. An uneventful recovery followed and when the woman was examined late in June the cervix was entirely healed and the uterus freely movable. Sufficient time has not elapsed to be certain of cure.

DIAGNOSIS

It is possible for the cancer to reach an advanced stage without giving any symptoms. Every experienced gynecologist has seen cases of carcinoma of the cervix in nonpregnant women who have had no symptoms which caused them to believe they were not wholly normal until the cancer had attained an advanced state of growth. In general, diagnosis during pregnancy is rather more difficult than at other times. This is

structed labor caused by the rigid undilatable cervix. In patients delivered vaginally at or near term Tagliaferro points out that the forceps offers a much better outlook for the infant than extraction by the breech. In the former the forceps serves in a sense, as he puts it, as a "protective helmet," while the after-coming head must be forcibly and rapidly brought through the rigid cervix. The best results for the child are obtained by abdominal cesarean section.

In pregnancies other than very early ones, a definite loss of fetal life follows the use of procedures done primarily in the mother's interest. Destructive operations and emptying of the uterus before viability cost a considerable number of fetal lives.

The infant of a markedly cachectic or severely toxic woman may be poorly developed. This will be seen only in advanced cases of cancer in women in late pregnancy. A case described by Cornil is referred to by Coroenne in which cancer was found in the thyroid, peritoneum, frontal bone and left patella of the child.

TREATMENT

The management of carcinoma during pregnancy has changed greatly in the course of the past fifty years. Amputation of the cervix, the removal of tumor masses which might obstruct labor, or cauterization were the only means of treatment at first available. As the mother had little chance for continued life, the chief attempt was to save the fetus. Interruption of pregnancy was found to be dangerous to the mother and was given up. Throughout the discussion available in the literature, experience has drawn a distinction between early and late cancers, or, between those which, when operative treatment is considered, are regarded as operable or inoperable. Again, a definite difference in efficiency of treatment has been noted between early and late pregnancies, or to divide the cases more exactly, those in the first six months and those in the last three. As to management during labor the early reports indicated that those cases which were allowed to go spontaneously into labor and to deliver, if possible, unaided, gave results far superior to those attained in cases terminated operatively, as by dilatation or incision of the cervix followed by extraction. Cohnstein, in 1873, for example, reports a maternal mortality of 50 per cent in cases in which incision of the cervix was employed, with a fetal mortality of 37 per cent. In a series of 9 cases in which craniotomy was done, 6 women died. It is apparent that an expectant management can succeed only in those cases in which the cervix is not so extensively invaded that it cannot dilate, and in which the tumor mass is not large enough to serve as a mechanical obstacle.

Cesarean section gave far better results for the child but many of the mothers died of infection and hemorrhage. The advent of the Porro

problem is considerably more difficult. Extensive ectropion or a more than normally firm consistency of the cervical tissue may cause carcinoma to be suspected when it is not present.

When carcinoma is accompanied by a very early pregnancy, the recognition of the latter may be difficult. The usual amenorrhea of pregnancy may be masked by the occurrence of bleeding caused by the cancer.

It is essential that the extent of the carcinomatous invasion be determined as exactly as possible in order that management may be most efficiently planned. In early pregnancy, if extension into the parametria has not taken place, mobility of the uterus may not be greatly lessened. In more extensive invasions with necrosis of the tumor surface, the lessened mobility of the uterus may be in part due to inflammatory exudate and not wholly to lateral extension of the cancer. If pregnancy is suspected and is not sufficiently advanced to render recognition easy, the Aschheim-Zondek or Friedman-Schneider tests are very helpful.

PROGNOSIS

The maternal prognosis has changed materially for the better in the past seventy years. Cohnstein found a mortality of 57.1 per cent in cases reported up to 1873. Chantreuil, quoted by Coroenne, collected 60 cases. Twenty-five of these women died in labor. The remainder died during the year of the labor or the following year. Theilhaber found a mortality of 31.5 per cent in the years intervening from 1873 to 1893. The mortality in the cases collected by Sarwey from 1898 to 1907 was 7.5 per cent. Of late years the increasing use of radiotherapy has lessened primary mortality. The increase in permanent cure has not been as striking as the decrease of primary mortality.

The prognosis for the mother is unfavorably influenced because of the rapid progress of the tumor during pregnancy, and during labor by tearing of the abnormal cervix, hemorrhage, and sepsis. During the puerperium the acceleration of tumor growth which is probably due to the trauma of labor again decreases the probability of cure. Early recognition and prompt utilization of radiotherapeutic and operative means have substantially increased the hope of cure. The extremely pessimistic attitude of Pinard and Champetier de Ribes, who considered every pregnant woman with cancer as doomed, irrespective of the type of treatment, is no longer justified.

FETAL PROGNOSIS

In early pregnancy many abortions occur, the fetus thus being lost. Surgical and radiotherapeutic measures utilized in the attempt to eradicate the cancer, sacrifice the lives of some infants and interfere with the normal development of others. In pregnancies which have gone to term, fetal life may be sacrificed or injury may occur because of ob-

made between radium and x-ray, or perhaps a combination of these. A combination of surgery and radiotherapy may be wise. The fate of the fetus must be decided. And finally, intelligent management depends upon an appreciation, as definite as may be, of the extent of the growth.

Operative removal is far more successful in early pregnancy. Peham and Amreich report six cures in a total of 19 cases, all of the cured patients having been operated upon in the first half of pregnancy.

Vaginal hysterectomy will naturally find a restricted application because of the relatively small number of operators who can work with facility by this route. Peham and Amreich favor abdominal hysterectomy, and this, except in early cases of limited extent, appears to be the most successful method.

In the first trimester, if operative management is chosen, radical hysterectomy is at once to be carried out without previously evacuating the uterus. The disease and the pregnancy are then at once disposed of. Previous evacuation increases somewhat the chance of diffusion of cancer cells. Operation should be followed by deep x-ray irradiation. If radiotherapy is chosen (and, unless the cancer is an exceedingly early one, this seems the preferable course), irradiation should be done irrespective of the pregnancy. This should be followed by deep x-ray irradiation or by the radium pack if this is available. The fetus will be killed and will probably come away spontaneously. If it does not the uterus may be evacuated six to eight weeks later. When x-ray is used, abortion is caused by alterations in the vessels of the placenta and cord. Abortion following radium is usually due to the capsule in the cervix, which acts as a foreign body.

In the second trimester, if the carcinoma is still operable, radical hysterectomy may be done if the surgical mode of attack is preferred. If irradiation is elected local irradiation by means of radium should be used followed by deep x-ray therapy. The fetus will be destroyed and may be expelled spontaneously later. If this does not occur the uterine body with its contents may be amputated, or if the extent of the lesion permits, complete hysterectomy may be done.

In dealing with Case 4, we quite deliberately evaded this rule simply because the carcinoma seemed to be sufficiently clean in a surgical sense that we might evacuate the uterus prior to irradiation with a fair degree of safety. This avoided the trauma to the cervix which would be caused by a later evacuation of the uterus through the birth canal or the necessity for later operation, and left the field clear for irradiation. It also avoided the possible disturbance of the carcinomatous area by a later operation and permitted the radiotherapy to proceed as in a nonpregnant case. While it succeeded in this case, and I should be inclined to do it again in a similarly favorable case, it cannot be recommended as a routine plan of management.

cesarean hysterectomy decreased the immediate death rate from sepsis but the maternal loss of life continued to be high from the cancer which remained and continued to grow.

Subtotal hysterectomy had another advantage, in that the removal of the uterine body prevented lochiometra due to closure of the cancerous cervix.

Vaginal hysterectomy was tried by Sarwey and a number of contemporary operators. It was found that, especially in the early months, it was rather more easily done than in nonpregnant women. This was due to the loosening of the fascial attachments of the uterus. It was carried out even in late pregnancy. Sarwey suggested that in the first trimester hysterectomy should be done without emptying the uterus, in the second trimester after emptying the uterus and in the third after vaginal cesarean section. Vaginal hysterectomy appears to have performed one service, for it proved that the earlier operative treatment is carried out, the better the chance of the mother.

The advent of the radical abdominal hysterectomy advocated by Ries and Wertheim brought a further and marked increase in the number of permanent cures. Its immediate mortality was greater than that of vaginal hysterectomy. This procedure came to be used more and more, vaginal hysterectomy occupying a continuously less important place. With the lessening of primary mortality and the increase in permanent cure there came necessarily to be less importance placed upon the life of the infant, unless it had, at the time of intervention, attained viability.

The increasing efficiency of radiotherapy again added to the success with which these difficult cases are managed. As late as 1928, however, Eymers said that the indications and value of this method could not be given. Portes and de Nabias, in cases in which viability had been attained, advised cesarean section, subtotal hysterectomy and irradiation of the carcinomatous stump. The use of any large amount of irradiation carries with it a distinct risk to fetal life, and irradiation in early pregnancy is followed by many abortions. Ikeda reported 7 cases in which irradiation was used in cancer in pregnant women. Two of these aborted and died. Five, irradiated in the sixth and seventh months, had spontaneous deliveries of normal children. Three of them became pregnant again and died of hemorrhage from lacerations of scars. One is disposed to wonder whether a recurrence had not occurred.

It seems agreed today that, except in patients who are quite hopeless, treatment shall be immediately instituted without regard to the child unless the child has attained viability. The choice of treatment is important. In Case 1 of those here reported, an unwise mode of attack was chosen. We had seen no previous case and were unfamiliar with other reported cases. If operative intervention is preferred the type of operation must be chosen. If radiotherapy is elected a choice must be

Extensive carcinoma either obstructs delivery completely, or allows the passage of the infant only at the expense of tears of the carcinomatous cervix. Serious hemorrhage, difficult or perhaps impossible to control, is the primary result with serious sepsis probable if the woman survives the labor. If the cancer is sufficiently extensive to be in any sense a problem during labor, delivery should not be attempted from below. Incision or dilatation of the cervix is extremely hazardous and should not be attempted. Two procedures are available. A Porro cesarean section may be done, with complete radiotherapy later. The operation will probably cause a wider diffusion of carcinoma, but it may be remembered that cure at this late stage of pregnancy is improbable in any event. The removal of the uterine body lessens the danger of peritonitis, which is very likely to follow simple cesarean section. Lochiometra is also prevented. The safety of the infant is far greater than if delivery is done from below.

Cesarean section may be done, followed by a Wertheim radical hysterectomy. This can be considered only if the cancer is within operable limits. It is a far more extensive procedure, and, in the greater number of cases, will not be possible. The Porro operation and subsequent irradiation are preferable. In patients operated upon too near the end of pregnancy the percentage of curability is so small that the assumption of a much greater primary operative risk does not seem wise.

CONCLUSIONS

1. The frequency of carcinoma in pregnancy, as estimated from several reports and including our own work, is 0.0321.

2. Pregnancy is unfavorably influenced. Abortions are frequent, placenta previa is more common than in normal pregnancy.

3. Labor may be gravely dangerous and is sometimes impossible.

4. Carcinoma is very rarely transmitted to the fetus, and, unless pregnancy terminates prematurely, it seems to develop as well as in other cases.

5. The results of treatment are far better during the first six months than in the last three.

6. Today irradiation, both by radium and deep x-ray, is the most effective treatment. This should be done at once unless the pregnancy is so far advanced that it is desired to allow the child to attain viability.

7. If full radiotherapy is used, the pregnancy is better terminated because of the risk of serious developmental harm to the infant.

8. A moderate radium dosage may be used to check the growth of the tumor in order that the child may attain viability with less likelihood of harm.

9. Labor may be permitted to begin spontaneously if the cervix has a sufficient uninvaded area to permit dilatation enough for the passage of the child.

In the last trimester results of treatment are less satisfactory than in the earlier cases. Upon this point all authors who have written upon the subject agree. Reports of operated cases show that cures are far rarer in late pregnancy than in the first half. In the seventh and eighth months of pregnancy it is well to wait until the child has attained a development which renders extrauterine life fairly possible before beginning treatment, whether this is to be operative or radiotherapeutic. This seems justified by the fact that at this stage of pregnancy the chance of permanently curing the mother by any means is not great. When this time has arrived, the uterus may be emptied and a subtotal hysterectomy done: in short, a Porro operation, with subsequent irradiation by radium and x-ray. Baer's suggestion merits attention. Not over 3,000 mg. hours of local irradiation by means of radium may be given, which will check the growth of the cancer until the child is viable. A Porro operation is then done, followed, after recovery, by complete radiotherapeutic treatment. This cannot be regarded as the best plan for the mother but will save an occasional infant. An alternative procedure is the radical Ries-Wertheim hysterectomy. This is available only when the extent of the growth permits its use. My own preference would be for the Porro operation followed by irradiation.

The reports of the effect of radium upon the fetus vary somewhat. Burnam reports 3 cases in which healthy infants were born after irradiation of a carcinoma of the cervix during pregnancy. Dosage is not stated. The opinion that radium is less harmful to the infant than x-ray is not borne out by the work of Goldstein and Murphy, who report a case of microcephalic idiocy in an infant delivered by a woman who was given 4,400 mg. hours of radium at six months' gestation. This child was followed for a number of years and remained an unteachable idiot. Petenyi reports a similar case after x-ray therapy; the child, however, was not observed over as long a time.

Goldstein and Murphy have collected 106 cases of women who were irradiated during pregnancy. Of these, 74 delivered full-term children. Thirty-eight (51 per cent) of these children showed disturbance of health or development of more or less serious nature. Sixteen of these children were microcephalic idiots. Fifteen of these mothers had been treated with radium. Radium therapy does carry with it a definite risk to the child *in utero*. Goldstein and Murphy believe that, if irradiation is used for carcinoma, the pregnancy should be terminated. Certainly figures like this cause one to hesitate in applying full radiotherapy unless the child is too far from viability to cause it to be an important consideration.

TREATMENT DURING LABOR

Cases of cancer of the cervix in women in labor divide themselves into two groups; those in which the cancer is small and involves only a portion of the cervix, and those in which the cervix is extensively invaded. If a sufficient amount of normal cervix remains to allow enough dilatation to permit the passage of the infant without serious injury to the cervix, labor may be allowed to complete itself spontaneously.

In labor at or near term, where there is a small lesion, spontaneous vaginal delivery should be permitted, followed by complete irradiation. In all other types of lesions of the cervix, Porro section should be performed at once with later irradiation. The less desirable alternative to this is cesarean section followed by the Wertheim operation and subsequent irradiation.

I believe we are ready to discard microscopic classification of carcinoma of the cervix as a guide to treatment. It would be a mistake to deprive a woman of irradiation merely because her squamous carcinoma is regarded as less radiosensitive than the anaplastic type. If an operative procedure is contemplated, it is important to culture the cervical secretions. If the *Streptococcus hemolyticus* is present, radiation must come first.

DR. GEORGE H. GARDNER.—There is still some question whether pregnancy actually has a stimulating effect on carcinoma. According to Stoeckel, who observed only 8 carcinomas in 15,000 pregnant women, nothing was observed after operating on these women which would warrant an assumption that the pregnancy either retarded or hastened the growth.

Since bleeding begins rather early and tends to be free and since most expectant mothers recognize the seriousness of any vaginal bleeding during pregnancy, there is ample opportunity for an early diagnosis and most of these carcinomas must be relatively early lesions, otherwise the woman probably would not have become pregnant. Often the lesion looks worse than it actually is because of the effect of pregnancy hyperemia.

Our experience at Passavant Hospital included only two such cases:

The first, a thirty-nine-year-old multipara, presented a large fibroid, a five months' pregnancy, and a carcinoma, apparently localized to the cervix. She was subjected to complete hysterectomy. Glands were found in the left iliac chain but were not removed. Subsequently she was given deep x-ray radiation. Apparently this therapy was too intensive because she died a year later of an agranulocytosis which was believed to have been induced or aggravated by the x-ray. At autopsy the glands were found to be somewhat larger than at operation and contained metastatic cancer.

The second patient was only thirty years of age. Her cervix was involved by an earlier lesion and her pregnancy was of three months' duration. Dr. Curtis performed a radical Wertheim operation. Although the uterus was freely movable glands were found in the left parametrium and were removed. This patient is receiving deep x-ray radiation and there is no evidence of recurrence, ten months after operation.

DR. HERBERT SCHMITZ.—I would like to add two cases to the series. At Mercy Hospital in 770 carcinomas of the cervix two occurred in pregnant women. One was twenty-eight years of age, a para ii, with a clinical Group III lesion in the last trimester of pregnancy. The other was aged thirty-six, para iv, a clinical Group IV lesion. Both of these were treated by cesarean section. Viable children were obtained and the carcinoma was then treated by extensive radiation therapy.

One must, however, be careful in the collection of these cases because in discussing the problem with Dr. Horner I find that he had also seen both of the cases reported above.

DR. F. H. FALLS.—I have seen three of these patients. The first was at Cook County Hospital in 1921. This patient entered the ward with a diagnosis of placenta previa. A living baby was delivered by cesarean section. The patient recovered and was sent to the tumor clinic for further treatment.

The second patient entered the clinic also as a case of placenta previa, for she had had severe painless bleeding about the seventh month. She was subsequently delivered at another hospital by cesarean section, at which time the carcinoma was

10. Incision or dilatation of the carcinomatous cervix is gravely dangerous.

11. If labor is not possible, cesarean section should be done as an elective measure. This should be followed by a Ries-Wertheim radical hysterectomy or subtotal hysterectomy with irradiation of the carcinomatous stump. The latter is favored.

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DISCUSSION

DR. JOSEPH L. BAER.—As a basis for treatment, the carcinoma must be regarded as primary and the pregnancy as a complication, just as with other diseases complicated by pregnancy.

The outstanding treatment in any carcinoma complicated by early or late pregnancy is adequate and competent irradiation. This means 3,000 to 4,000 mg. hr. of radium to the cervix with the same amount of pelvic irradiation or an equivalent amount of deep x-ray therapy.

This treatment in early pregnancy will result in death of the fetus and termination of the pregnancy by abortion, spontaneous or operative. After viability the treatment produces in 40 per cent of the cases fetal defects, such as alopecia, microcephaly and idiocy. Hysterotomy or primary induction of abortion to evacuate an early pregnancy, or cesarean section to rescue a viable fetus while retaining the carcinomatous uterus, has a high mortality, even with subsequent irradiation.

The following condensed outline of treatment is offered: If the pregnancy is less than four months, complete irradiation is safest, regardless of the extent of the carcinoma. Spontaneous abortion usually follows. If not, the uterus can be emptied subsequently, for the irradiated cervix offers little resistance to dilatation. Occasionally, when the lesion is clinically merely suspicious, but is confirmed by biopsy and there is no involvement of the deeper cervix, a skilled operator may attempt radical surgery with subsequent radiation.

If the pregnancy is somewhat less than seven months, the lesion belongs to the clinical Group I and the mother wants the child, it is wise to use local irradiation only. That temporarily stops the disease. When viability is attained, Porro section and then irradiation are indicated. In all other types of lesions with a pregnancy of four to seven months, complete irradiation is advised. Thereafter if spontaneous evacuation of the uterus does not occur supravaginal hysterectomy with removal of the adnexa should be undertaken. When the pregnancy is between seven and nine months and the lesion belongs to clinical Group I, a Porro section should be done with retention of the cervix followed by complete irradiation. In all other types of lesions, preliminary local irradiation of the cervix to minimize infection and retard spread of the carcinoma should be given followed by Porro section, and then final irradiation.

The application of the above, and similar experimental observations on laboratory animals, to the treatment of the human patient in gynecologic practice is beset with many pitfalls. The repeatedly demonstrated species differences in the response of various laboratory animals to endocrine preparations cannot but engender misgivings in the mind of the conscientious gynecologist who is striving to apply these newer experimental findings on animals to the treatment of the ailments of the human female. It need hardly be emphasized that it behooves the science of gynecology to keep pace with the progress of endocrinology, by obtaining direct evidence of the applicability of the latter to the human subject, by the use of similar objective experimental methods.

In accordance with these considerations Moir⁹ studied the motility of the puerperal human uterus by introducing a rubber bag connected by rubber tubing to a recording device. More recently, Falls and two of the present authors¹⁰ have reported studies on the effects of estrogenic substance and of progesterone on the human puerperal uterus, using the method described by Moir. This work was consistent with previous reports of similar studies in laboratory animals and objectively confirmed our clinical impression that progesterone was of value in the treatment of threatened abortion through its inhibitory action on uterine contractions.¹¹ Lubin and Clarke¹² have since utilized this principle in treating afterpains with progesterone, in a large group of puerperal women, and have obtained relief in about 90 per cent of their cases.

In applying the above to the treatment of certain disorders in the nonpregnant and nonpuerperal woman, it seemed desirable to obtain experimental evidence as to whether or not the nonpregnant and nonpuerperal human uterus reacted identically with the puerperal organ. Partly because of the greater technical difficulties involved, few experimental studies on the motility of the human nonpregnant and nonpuerperal uterus have been made.

Moir¹³ applied his method of recording contractions of the puerperal uterus on a miniature scale to the nonpuerperal uterus. He constructed a small rubber bag on the end of a hollow sound which could be introduced into the uterine cavity. He was able to record rhythmic contractions produced by the uterus by connecting the small uterine bag with a Huthke manometer. These contractions were frequent, regular, and small during the first half of the menstrual cycle. After the sixteenth day they became increasingly stronger but less regular. He was able to produce a spasmodic contraction of the uterus with intramuscular injections of pituitary extract, irrespective of the stage of the menstrual cycle. These observations are contrary to those made by Knaus.¹⁴ The latter used a similar method to study the response of the human uterus to intravenous injections of pituitary extract. He found that during the first fourteen days of the menstrual cycle the regular rhythmic contractions showed an increase in muscular tone forty to fifty seconds after the administration of pituitary extract. Knaus reported that after the sixteenth day, the uterus exhibits a decreased capacity for spontaneous contractions and becomes flaccid and sluggish with a completely negative pituitary reaction. This state continues until twenty-four hours before the onset of menstruation when

discovered. She re-entered our hospital for treatment of the carcinoma with radium and x-ray but did not respond favorably.

The third patient entered the clinic as an incomplete abortion. The right side of the cervix was extensively involved in a carcinomatous mass. I cauterized the carcinoma with a Percy cautery, and followed with radium and x-ray treatments. The patient was alive two years later.

If we are to make progress in the treatment of cancer of the cervix, we should not wait until bleeding begins before making a diagnosis. We should study the cervix of every pregnant woman for the possible presence of carcinomatous or precarcinomatous lesions. We should use the colposcope and paint every cervix with Lugol's solution at least once during the pregnancy, and certainly inspect and paint with Lugol's solution all patients in whom even slight bloody spotting occurs. Thus we may locate some of these tumors at a time when removal is still possible.

DR. DANFORTH (in closing).—The figures published by Dr. Baer are quite close to those that I found. One carcinoma in a hundred is complicated by pregnancy. His incidence of carcinoma in pregnancy, 1 in 10,000 does not vary much from what we found.

The single case of metastasis in the tissues of the child was the only one in the literature and was found in a French thesis published in 1873. We can assume that that is exceedingly rare. The papers which have appeared in the last thirty-five years indicate that in the opinion of most observers pregnancy does make carcinoma grow more rapidly.

Dr. Falls spoke about the use of the method of Schiller for early diagnosis. If it were possible during pregnancy, it would be very desirable. There is nothing in the literature which indicates that it has been tried. The discoloration of the cervix, which is part of the pregnancy picture, might interfere with the color contrast upon which the test depends. It would be an interesting thing to try, but I would be skeptical until I had tried it.

DR. FALLS.—I have done that within the last week. It shows up very beautifully.

THE EFFECT OF THE OVARIAN HORMONES ON THE HUMAN (NONPUERPERAL) UTERUS*

LEON KROHN, M.D., JULIUS E. LACKNER, M.D., AND
SAMUEL SOSKIN, M.D., CHICAGO, ILL.

(From the Department of Gynecology and Obstetrics and the Department of Metabolism and Endocrinology of Michael Reese Hospital)

THE physiologic effects of the ovarian hormones on the uterus of the experimental animal have been well established. It is known that the estrogenic principle and progesterone are antagonistic in their effects on uterine motility. The estrogenic hormone enhances the rate and amplitude of uterine contractions,^{1, 2} probably by sensitizing the uterine muscle to the oxytocic principle of the pituitary gland.^{3, 4} Progesterone has been shown to decrease the activity of the uterus,⁵⁻⁷ and to inhibit the normal response of the uterine muscle to the oxytocic principle of the posterior pituitary gland.⁸

*Read before the Chicago Gynecological Society, November 20, 1936.

a threaded projection which screws into a corresponding inside thread in the end of the catheter. A number of perforations are made along the wall of the catheter for a distance of 4 cm. from the tip. The balloon proper consists of a piece of penrose tubing, one end of which has been smoothly sealed. With the tip of the catheter removed, the penrose tubing is pulled over the end of the catheter. The metal tip is then screwed into place through a small perforation in the sealed end of the penrose tubing. The joint is made tight with rubber cement. The open end of the penrose tubing is then firmly closed around the body of the catheter, beyond the perforations, by the use of strips of thin rubber sheeting and rubber cement. The lumen of the catheter now communicates with the interior of a closed balloon by way of the perforations in the catheter wall. The catheter running through the balloon gives it the necessary rigidity for insertion into the uterus.

The method of recording the variations in volume and pressure of the rubber balloon was devised by one of us (S. S.) and has not been hitherto described. The leveling tube (*B*) consists of a straight 10 c.c. pipette, calibrated to tenths of a cubic centimeter from which the tip has been removed. The water manometer (*C*) consists of a narrow arm (8 mm. inside diameter glass tubing) which communicates through rubber pressure tubing with the leveling tube (*B*) on the one hand, and through the stopcock (*D*) to the air. On the short end of the narrow arm a wide glass tube (20 mm. inside diameter) is affixed by means of a rubber stopper. Into this wide tube is loosely fitted a balsa-wood float coated with celluloid (*E*). Wire pins circumferentially placed around the top and bottom of the float act as guides and prevent surface tension interference. The top of the wide glass tube carries a metal cap (*F*) from the side of which an upright projects. The tip of this upright serves as the fulcrum for a light recording lever.

To operate the apparatus, the balloon (*A*), catheter and connecting tubing up to the leveling tube (*B*) are filled with water and all air bubbles are eliminated. The manometer (*C*) is filled with water until the float (*E*) rides freely. The stopcock (*D*) is left open to the air. By raising the balloon (*A*) above the level of the leveling tube (*B*), it is caused to collapse as far as possible. A pinchcock is placed on the rubber tubing leading into the catheter. The balloon (previously sterilized) is now inserted into the uterus of the subject, and is held in place by an elastic band by which it is anchored to a single vulsellum placed in the anterior lip of the cervix. The movable scale (*G*) is adjusted so that its lowest point is at the level of the uterus. The level of the meniscus in the leveling tube (*B*) is noted. The pinchcock is removed from the rubber tubing leading to the balloon. The latter fills according to the capacity of the uterus. The position of the leveling tube (*B*) is now adjusted until the water meniscus within it is at the level of the point on the scale (*G*) which indicates the pressure at which it is desired to make the observations. The level of the meniscus in the leveling tube (*B*) is again noted. The difference between this and the previous reading (plus the volume of the intrauterine portion of the catheter and the balloon as a correction) gives the intrauterine capacity. The stopcock (*D*) is now closed, and the manometer begins to record uterine motility, at a known volume and pressure. To quantitate the records in cubic centimeters of volume change, the manometer is calibrated in the conventional manner.

The extraction of the blood for the estrogenic and gonadotropic hormones was made on a single specimen of blood according to the method described by Freed.¹⁶ In this procedure acetone is used to precipitate the whole blood. The fat-soluble estrin remains in the supernatant acetone while the water-soluble gonadotropic hormone is easily extracted from the precipitated proteins by acidified 50 per cent alcohol.

The urine was extracted for estrogenic substance only, since it has been shown that the amount of gonadotropic hormone (prolan) in the urine parallels that in the blood.¹⁷ The twenty-four-hour urine specimen was divided in two; one-half

the uterus again behaves as it did during the first fourteen days of the cycle. He attributes the failure of response to pituitary extract during the last half of the cycle to the formation of the corpus luteum and liberation of the corpus luteum hormone. It was by this method that Knaus estimated the time of ovulation.

Falk and Nahon¹⁵ obtained tracings of human uterine contractions by using a direct electrical "lead off" from the uterus through the electrocardiograph. They found a definite increase in activity from the ninth to the eighteenth day of the menstrual cycle. Repeated injections of theelin seemed to augment the waves irregularly.

We wish to report some observations on the effects of estrogenic substance* and of progesterone† on the human nonpregnant and nonpuerperal uterus, in normal women and in women suffering from certain endocrine disorders.

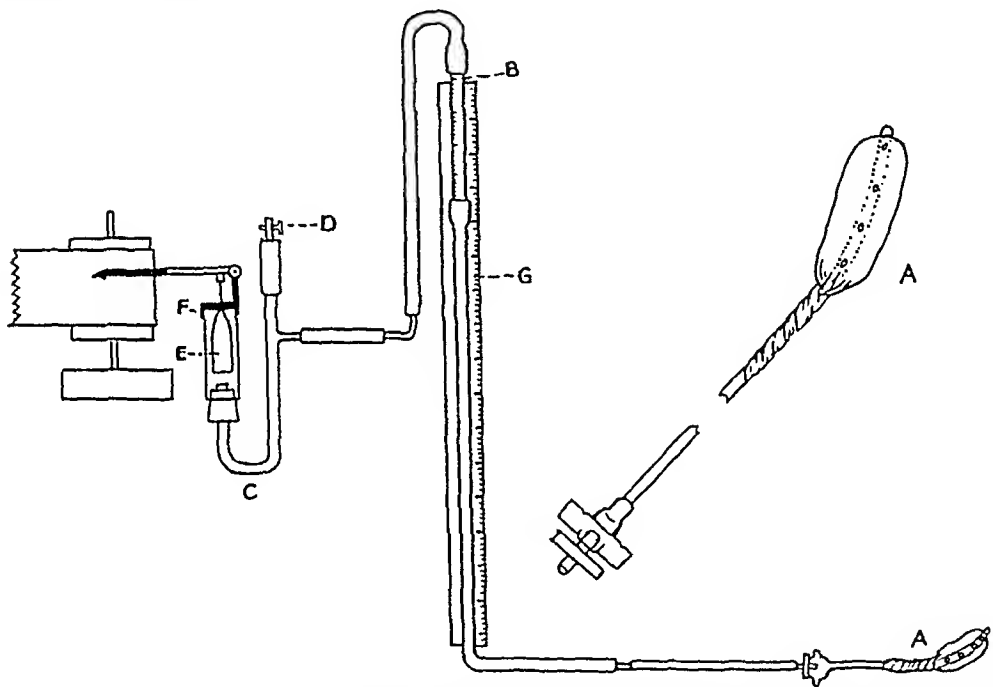


Fig. 1.—Apparatus for recording uterine motility at known volume and pressure. (A) Balloon ensemble, (B) calibrated leveling tube, (C) water manometer, (D) stopcock, (E) Balsa-wood float, (F) metal cap supporting the recording lever, and (G) movable scale.

PROCEDURE

In a small group of selected cases three modes of investigation were simultaneously followed at various intervals in the menstrual cycle of each subject. The motility of the uterus was quantitatively recorded, and on the same day that each tracing was made, endometrial biopsies were taken and blood and urine specimens were collected for determination of hormone content.

Uterine motility was recorded with the apparatus diagrammatically represented in Fig. 1. It consists essentially of a rubber balloon (A) for insertion into the uterus, a calibrated leveling tube (B), and a water manometer (C).

The balloon ensemble (A) is made from a metal uterine insufflation catheter the end of which is occluded by a rounded metal tip. The tip is held in place by

*Progynon B (Schering).

†Proluton (Schering).

cycle and on the first day of menstruation following the intramuscular injection of 10,000 International Units of estrogenic substance* given daily for five consecutive days prior to the onset of menstruation.

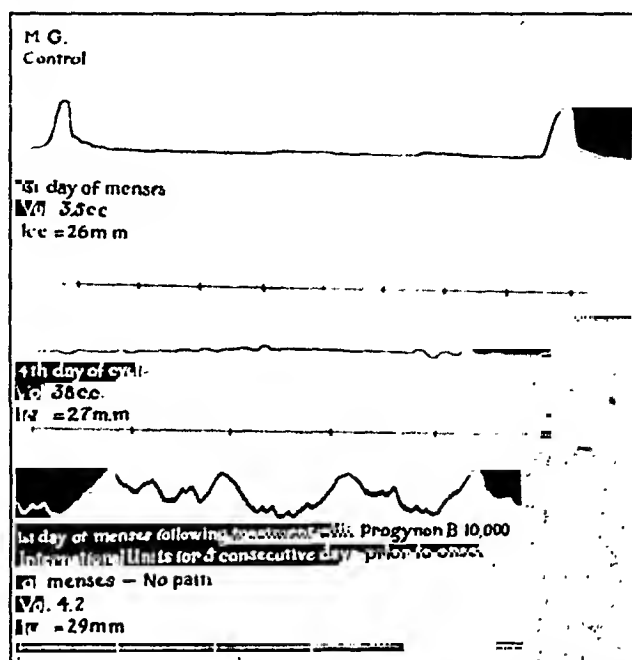


Fig. 3.—Uterine motility in a normal control, before and after the administration of estrogenic substance. (Photographic reduction $4\frac{1}{2}$ times.) Recording pressure 100 cm. of water.

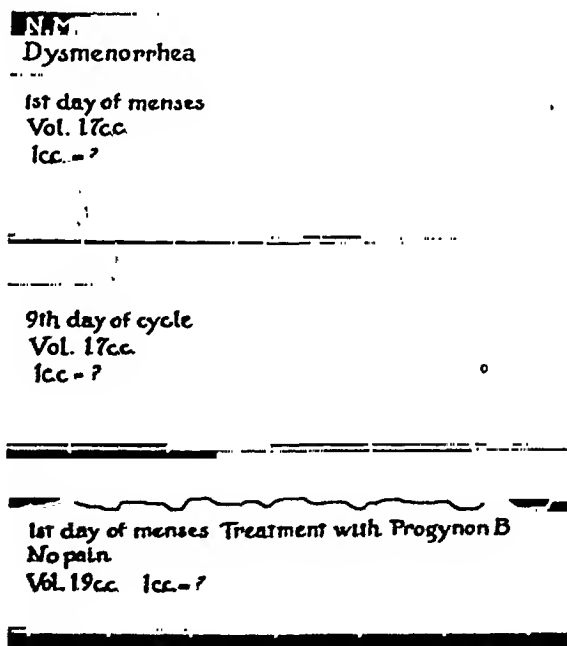


Fig. 4.—Uterine motility in patient with oligomenorrhea and dysmenorrhea following bilateral resection of ovaries, before and after treatment with estrogenic substance. (Photographic reduction $2\frac{1}{2}$ times.) Recording pressure 100 cm. of water.

CASE 3.—(Oligomenorrhea and Dysmenorrhea, Fig. 4.) N. M., aged twenty-nine years, para 0, gravida 0. Dysmenorrhea and oligomenorrhea following bilateral resection of polycystic ovaries three years ago for amenorrhea. Uterus small and movable. No palpable adnexal pathology. Studies made on the first and ninth

was extracted by the tungstic acid precipitation method¹⁸ for free estrin and the other half was extracted for total estrin by preliminary acid hydrolysis and subsequent tungstic acid precipitation.¹⁹

Castrated mice were used for the assay of blood estrin, the test being called positive if the extract from 40 c.c. of blood produced a cornified smear in one mouse in forty-eight to sixty hours, signifying at least 25 M.U. per liter. The gonadotropic hormone was assayed on infantile rats, the test being called positive if the extract from 40 c.c. of blood produced an Aschheim-Zondek reaction in twenty-three- to twenty-five-day-old rats in one hundred hours.

The urinary estrin was assayed on castrated mice, also. Since there seems to be considerable variation in the actual amount of estrin corresponding to a mouse unit, depending on the strain of mice and the technique of assay, we have converted our mouse units into International Units. In our laboratory one mouse unit equals three International Units.

The endometrial biopsies were obtained with Novak's suction curette.²⁰

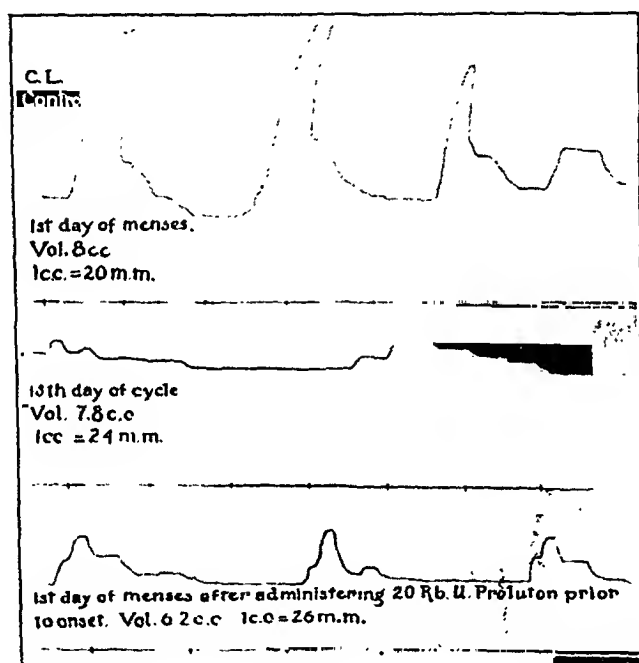


Fig. 2.—Uterine motility in a normal control, before and after the administration of progesterone. (Photographic reduction $4\frac{1}{2}$ times.) Recording pressure 100 cm. of water.

The following group of selected cases was studied. Illustrative graphic records are presented for each case (Figs. 2 to 6) and the results are summarized for purposes of comparison in Table I.

CASE 1.—(Normal Control, Fig. 2.) C. L., aged twenty-one years, para ii, gravida ii. No complaints, menstrual history normal, normal genital status, no previous operations. Studies were made on the first and fifteenth days of the menstrual cycle and on the first day of menstruation following the intramuscular administration of 5 European rabbit units of progesterone* given daily for four consecutive days prior to the onset of menstruation.

CASE 2.—(Normal Control, Fig. 3.) M. G., aged twenty-three years, para i, gravida i. No complaints, menstrual history normal, no previous operations, normal genital status. Studies were made on the first and fourteenth days of the menstrual

*Proluton (Schering).

TABLE I

CASE	AGE	PARA	MENSES	DIAGNOSIS	DAY OF CYCLE	HORMONE ADMINISTERED	UTERINE MOTILITY	UTERINE VOLUME	BLOOD		URINE ESTRIN	ENDOMETRIUM
									PRO-LAN	ES-TRIN		
1 C. I.	21	ii	Normal	Normal	1st day of menses	None	Extremely large contractions. Regular, 1 every 2 minutes	8 c.c.	+	0	Free 30 Total 120	Cervical epithelium and glands
					15th	None	Moderate contractions Irregular in size and frequency	7.8 c.c.	0	0	Free <30 Total <30	Proliferating
					1st day of menses	Proluton 20 Rb.U.	Moderate contractions Regular, 1 every 2 minutes	6.2 c.c.	0	0	Free 30 Total 30	Early secretory
2 M. G.	23	i	Normal	Normal	1st day of menses	None	Moderate contractions Regular, 1 every 5 minutes	3.5 c.c.	0	0	Free 30 Total 30	Secretory
					14th	None	Small contractions Irregular	3.8 c.c.	0	0	Free <30 Total 60	Proliferating
					1st day of menses	Progynon B 50,000 I.U.	Moderately large contractions. Regular, 2 to 3 per minute	4.2 c.c.	0	0	Free <30 Total <30	Secretory
3 N. M.	29	0	Dysmenorrhea Oligomenorrhea Flow scant Lasts 2 days	Dysmenorrhea Oligomenorrhea	1st day of menses	None	No contractions	1.7 c.c.	0	0	Free 60 Total 60	Specimen insufficient
					9th	None	No contractions	1.7 c.c.				Specimen insufficient
					1st day of menses	Progynon B 100,000 I.U.	Small irregular contractions—1 to 2 per minute	1.9 c.c.	0	++	Free 20 Total 180	Late proliferating

days of the menstrual cycle and on the first day of menstruation following intramuscular injections of 10,000 International Units of estrogenic substance* three times a week for one month prior to the onset of menstruation.

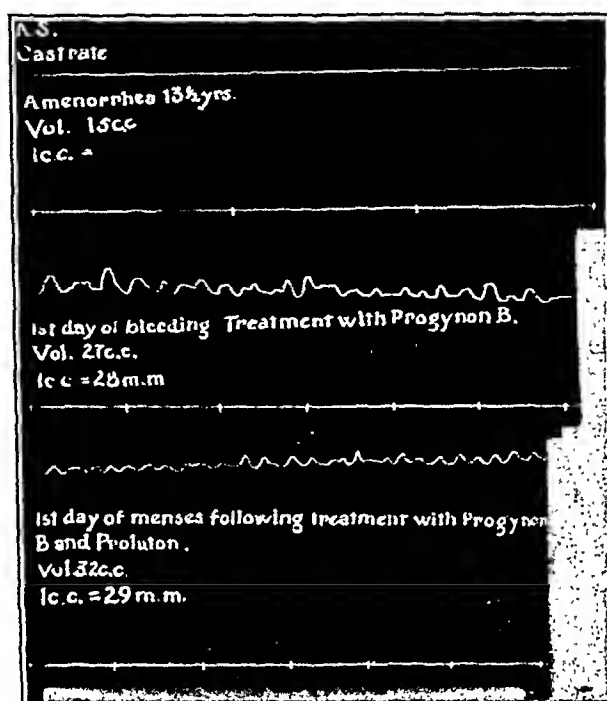


Fig. 5.—Uterine motility in a castrate, before and after treatment with estrogenic substance alone, and with estrogenic substance plus progesterone. (Photographic reduction 4 times.) Recording pressure 100 cm. of water.

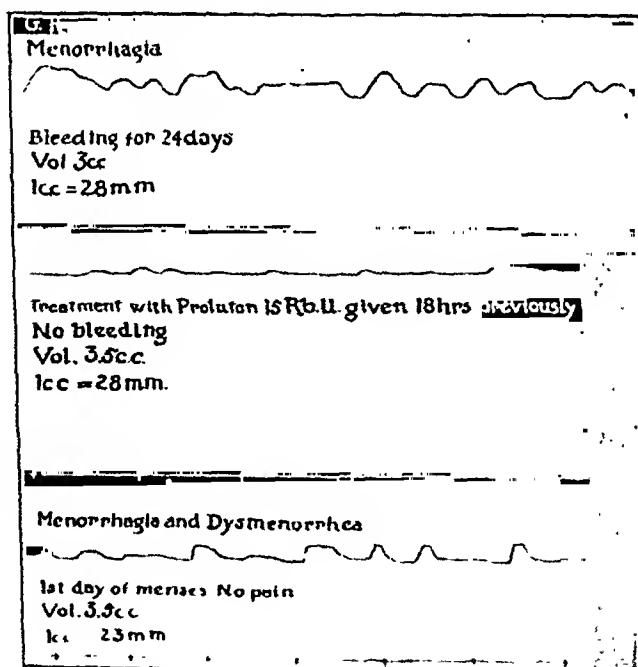


Fig. 6.—Uterine motility in patient with menorrhagia and dysmenorrhea, before and after treatment with progesterone. (Photographic reduction 4 times.) Recording pressure 100 cm. of water.

CASE 4.—(Castrate, Fig. 5.) A. S., aged thirty-one years, para 0, gravida 1. Spontaneous miscarriage in 1921. Bilateral salpingo-oophorectomy fourteen years ago

followed by amenorrhea. Uterus atrophic. No palpable adnexa. Studies were made before therapy was instituted, on the first day of bleeding following intramuscular injections of 10,000 International Units of estrogenic substance* three times a week for three weeks, and on the first day of bleeding produced by a similar course of estrogenic substance* which was followed by one injection of five European rabbit units of progesterone,† twenty-four hours later.

CASE 5.—(Functional Menorrhagia and Dysmenorrhea, Fig. 6.) G. K., aged twenty-five years, para 0, gravida i. Spontaneous miscarriage at six and one-half months in February, 1935. Appendectomy in 1928. Menses profuse since onset lasting seven to twenty-one days with pain on first day. First studies made while patient was flowing and had been bleeding for twenty-four days. Was then given fifteen European rabbit units of progesterone.‡ The bleeding stopped eighteen hours later and the studies were repeated. Two months later similar observations were made on the first day of a normal menstruation.

DISCUSSION OF RESULTS (TABLE I)

There is a wide range in the motility of the uterus of normal patients at corresponding times of the menstrual cycle. The uterus is usually quiescent during the midperiod, but the motility at this time may vary in normal patients from no contractions to moderate sized contractions. The maximum motility is on the first day of menstruation. The strength of the contractions seems to be in direct proportion to the size and volume of the uterus in women with a normal hormonal balance. Thus, in Case 1 (Fig. 2), the volume of the uterus was large and the contractions on the first day of menstruation were very intense, although the patient suffered no discomfort whatsoever. This patient was selected to demonstrate the inhibitory action of progesterone because of the large size of these contractions. At the subsequent period after the administration of twenty European rabbit units of progesterone, the contractions were less than one-third of their former size.

The volume of the uterus in Case 2 (Fig. 3) was relatively small. The contractions on the first day of menstruation were only moderate in size but after the administration of 50,000 International Units of estrogenic substance they were markedly increased both in intensity and frequency.

These two cases offer an excellent contrast between the actions of the two ovarian hormones in normal women. They demonstrate that the normal human nonpregnant and nonpuerperal uterus reacts to these hormones in a manner similar to the response of the human puerperal uterus, and of the uterus of laboratory animals.

Case 3 (Fig. 4) presents a typical example of a deficiency of the estrogenic principle. The uterus was small and the patient's menses were scant and painful. No spontaneous motility could be demonstrated either at the mid-period or on the first day of menses. However, after

*Progyron B (Schering).

†Proluton (Schering).

‡Proluton B (Schering).

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DISCUSSION

DR. FRED H. FALLS.—The importance of this paper lies in the fact that the observations made were recorded by instruments of precision and could not have been influenced by any bias which the investigators may have had toward the results of the experiments. This puts the use of these hormones on a rational basis.

When one injects the estrogenic hormone or progesterone different physiologic reactions can be noted and measured. However, as these investigators have pointed out, one has to be careful in the interpretation of the phenomena observed, since certain reactions might conceivably be the result of coincidence. For instance, in the case of bleeding which was produced in the uterus years after a castration, one would like to know how many times was this woman made to bleed? Were subsequent injections successful or not? How long was this patient observed? How many cases of each type were treated successfully? Were some cases encountered which did not respond at all to injections?

In our experience, the most striking effect of the use of progesterone has been in controlling menorrhagia and metrorrhagia occurring in young girls shortly after menstruation begins. We have had two cases which responded favorably to progesterone after follutein had been tried and had proved only temporarily efficacious. We have had one patient with a severe purpura hemorrhagica, in whom various forms of endocrine therapy had been used unsuccessfully, before progesterone produced a definite effect.

The tracings here presented are far better than those of Knaus, whose contraction curves were very small. We have found that by using a water manometer instead of a mercury manometer, we were able to get very delicate tracings of the effect of pitressin on the large bowel, using the method of Moir, with the bag inserted in the rectum.

Another important point is that the data here presented relate to the effects of these substances on the human uterus and are, therefore, not analogies drawn from observations made on animals.

DR. S. SOSKIN.—It is true that the contractions of a large uterus can be recorded with a less elaborate manometer than we used. Our apparatus, however, records the motility of a small, nonpuerperal uterus with equal facility, and yields more quantitative data, since it operates at a known volume and at a constant known pressure.

intensive therapy with estrogenic substance, small, irregular contractions appeared. This was associated with a strongly positive estrin determination in the blood and a marked increase of estrin in the urine. The menstrual period increased from two to five days and the quantity was more profuse. There was no pain accompanying this period.

In the case of the castrated woman (Case 4, Fig. 5) the uterus was atrophic and no motility could be demonstrated. Intensive treatment with estrogenic substance produced an artificial bleeding and small rhythmic contractions. Therapy with estrogenic substance and progesterone also produced an artificial bleeding with small contractions of the uterus. The atrophic endometrium became hyperplastic. The volume of the uterus approximately doubled.

The case of functional menorrhagia (Case 5, Fig. 6) is an example of a deficiency of progesterone. A uterine hemorrhage of twenty-four days' duration was stopped in eighteen hours with fifteen European rabbit units of progesterone. This therapy also produced a decrease in the motility of the uterus. The endometrium changed from a proliferative to a late proliferative type.

The results of the administration of estrogenic substance or progesterone to the latter three patients indicate that the use of the appropriate hormone as substitutional therapy in women suffering from endocrine deficiencies is a rational attempt to bring about a temporary return toward the normal physiologic and clinical state.

CONCLUSIONS

1. A method for recording the motility of the human nonpuerperal and nonpregnant uterus is described.
2. The method is harmless and is of value in the study of endocrine disorders of the female.
3. The normal human uterus is quiescent at the mid-period and its motility is greatest at the onset of the menstrual period.
4. Estrogenic substance augments the motility of the normal human nonpregnant and nonpuerperal uterus; progesterone decreases the motility.
5. Estrogenic substance induced motility and initiated bleeding in the uterus of a woman castrated fourteen years previously. It induced motility, increased menstruation, and relieved dysmenorrhea in a woman with bilaterally resected ovaries. Progesterone decreased the motility and stopped the bleeding in a woman suffering from functional menorrhagia.

We are indebted to the Schering Corporation for ample supplies of progynon B and proluton; to Dr. Otto Saphir for generous cooperation with the histologic interpretations; and to Dr. S. Charles Freed for the performance of the arduous task of assaying many samples of blood and urine for their hormone content.

PYELOURETERITIS IN PREGNANCY*

ETIOLOGY, ACUTE PHASE AND TREATMENT

HERBERT F. TRAUT, M.D., NEW YORK, N. Y.

(From the Department of Obstetrics and Gynecology, New York Hospital and Cornell Medical College)

PYELITIS as a complicating disease of pregnancy has been recognized and treated for many years, but despite this fact it has been one of the least understood of the obstetric diseases. It is difficult to explain why this should have been so. However, it should be true no longer, for recently much new light has been shed upon the physiology of the ureter in pregnancy and the etiology of pyelitis, on the one hand; while on the other, diagnostic methods and the treatment of the disease have been improved, and we have gained an understanding of the sequelae of pyelitis in the woman and her offspring. This new information has necessitated a complete revision of our ideas concerning the significance of pyelitis in pregnancy, with the result that whereas formerly we were inclined to classify it as one of the minor complications, we are now forced to consider it among the more important. Many of the data which have brought about this change in point of view have been obtained by means of improved methods of urologic diagnosis. More important, however, has been the accumulated information which has resulted from cooperation between urologists and obstetricians in obstetrical hospitals both in this country and abroad. We shall attempt to present the subject of pyelitis as a complicating disease of pregnancy and the puerperium in the light of the more recent developments.

As some confusion has been occasioned by differences in terminology, it may be well at the outset to indicate what is meant by some of the commoner terms in this field. As the name indicates, pyelitis is an inflammatory disease affecting the pelvis of the kidney. However, when the renal pelvis is inflamed the ureter is usually involved as well; hence it is more accurate to use the term pyeloureteritis instead of pyelitis. If the infection extends from the renal pelvis into the parenchyma so as to involve the ducts and secretory elements of the kidney, one speaks of pyelonephritis. In addition, other terms are used to indicate more advanced stages of the inflammatory process: pyonephrosis indicates a marked dilatation of the renal pelvis and abdominal ureter associated with a purulent inflammation. In distinction, one speaks of hydro-nephrosis and hydroureter when there is marked dilatation of the renal pelvis or ureter without inflammatory involvement being present (Fig. 1).

*Read at a meeting of the New York Obstetrical Society, January 12, 1927.

Other interesting aspects of this work are the great variability in the estrin and prolactin of blood and urine in normal individuals, and the poor correlation between these hormone contents and the clinical manifestations in patients suffering from endocrine dysfunctions. To those of us who have been looking forward to hormone-testing as an aid to clinical practice, this seems rather disappointing. But perhaps we can comfort ourselves by ascribing this apparent lack of correlation to the inadequacy of our present knowledge. In this regard you may be interested to know that Dr. Freed, of my department, and I are just reporting on the probable presence of at least four factors in the ovary, other than estrin or progesterone, which have to do with the menstrual cycle. There is apparently an inhibitory substance, an augmenting substance, a factor concerned with endometrial rhythm, and also a factor influencing breast development. When we have learned to test for such factors, in addition to those which we can now assay, we may then be in a better position to interpret the clinical status of our patients in quantitative hormonal terms.

DR. KROHN (in closing).—We attempted to emphasize the fact that the effects produced with the ovarian hormones were temporary in nature because the type of therapy was substitutional. We have made approximately eighty similar studies and have been able frequently to reproduce the results obtained in this selected group of cases.

Encouraging results are obtained with cases of functional menorrhagia when large doses of progesterone are administered (15 to 20 International Units). Unfortunately, there are some patients who do not respond to this form of therapy. It has been recently recommended that more satisfactory results are obtained with smaller doses of progesterone if a preliminary dilatation and curettage is done.

We were unable to confirm the observation made by Moir, of the disappearance of the arterial pulsations at the peak of the contractions obtained from a patient suffering with dysmenorrhea. In a recent study of a group of dysmenorrheic patients, we frequently observed these pulsations continuing throughout the peak of the contractions. We, therefore, cannot agree with the suggestion that pain in primary dysmenorrhea is due to an ischemia of the uterus.

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After discussing the literature on hysterosalpingography, the authors present their own material, which embraces 55 cases. Fifty-one of these were examined on account of sterility, and 4 for other reasons. They report, in addition, a case where radiograms placed at their disposal illustrate injection into the venous system. In the experience of the authors, the method is extremely valuable. With strict indications and correct technical application it entails very little risk and gives valuable information. In no less than 25 per cent of the normal cases (28), the method proved curative, pregnancy having followed within a few months.

In order, however, to make the method wholly effective diagnostically, the authors perfected their roentgen technique so that, in cases where pathologic changes of the pelvic organs are visible, the roentgen examination is made with the patient in different positions using in addition to the dorsal, the lateral, upright, and upside-down positions. The effect of this procedure has been very satisfactory.

J. P. GREENHILL.

per cent of all women, x-ray photographs made during the seventh and eighth months of pregnancy disclose a dilatation of the ureter and kidney pelvis. This hydronephrosis and hydroureter are unmistakable evidences of stasis of urine. We may say, therefore, that 80 per cent of all pregnant women are predisposed to pyeloureteritis in the sense that they are always possessed of one of the important etiologic factors of the disease.

It is also significant that this stasis of urine is much more frequent and more marked on the right side than on the left, and furthermore, that with corresponding frequency the infection of the upper tract is on the right side rather than the left. As a result of the recent investigative work done in this field, we are enabled to make definite statements regarding the causes of urinary stasis in pregnancy. Most fundamental of these is muscular atony. It has been shown that the smooth muscula-

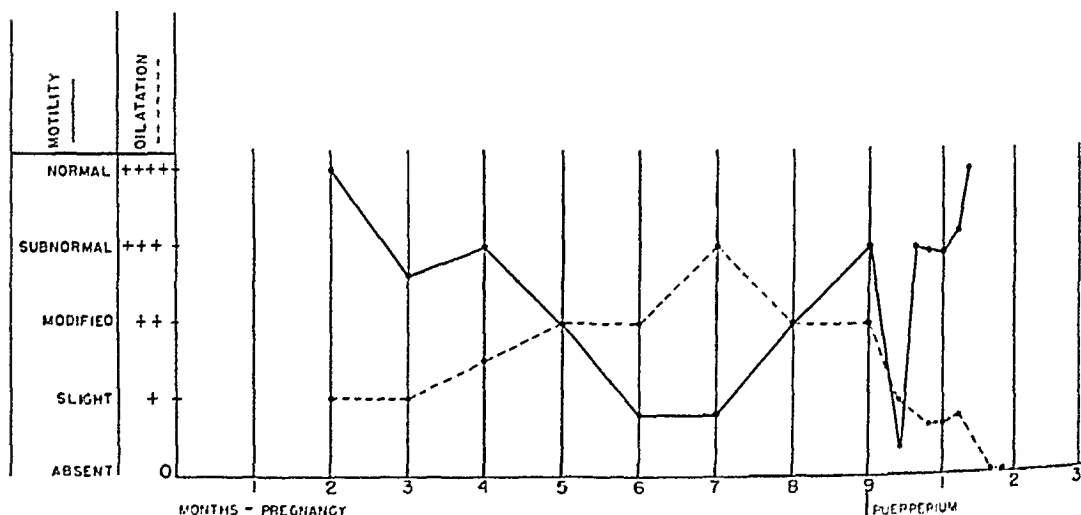


Fig. 2.—A composite graph made from the data obtained from the study of fourteen normal pregnant women. The solid black line shows the variations in the peristaltic activity of the tract with reference to the duration of pregnancy and the puerperium. The interrupted line shows the degree of dilatation of the tract. It will be seen that in general they are inversely proportional, very strongly suggesting a causal relationship.

ture of the ureter responds to the influences of pregnancy in a manner very similar to that of the uterus. To be specific, the smooth muscle coats of the ureter lose much of their irritability from the third to the ninth months of pregnancy (Fig. 2). This means reduced contractility and loss of peristaltic activity, with the result that when the weight of the enlarging uterus encroaches upon the already atonic ureter, there is increased difficulty in discharging urine into the bladder. The urine, therefore, accumulates and distends the flaccid ureter and kidney pelvis, producing the hydroureter of pregnancy. In addition, the pregnant uterus usually rotates on its long axis toward the right. In doing so, it brings greater pressure to bear upon the right ureter than upon the left, which in turn produces more marked stasis and ureteral dilatation in

The incidence of pyeloureteritis as a complication of pregnancy is such as to rank it in importance with chronic nephritis and cardiac disease. Our experience at the New York Lying-In Hospital in 15,000 consecutive deliveries gives the following comparison:

	PER CENT
Pyelitis	2.02
Chronic nephritis	2.29
Cardiac disease	3.66

Not only does pyeloureteritis rank with chronic nephritis and cardiac disease in frequency but if neglected, the sequelae may also cause it to rank in importance with these diseases because of the impairment of

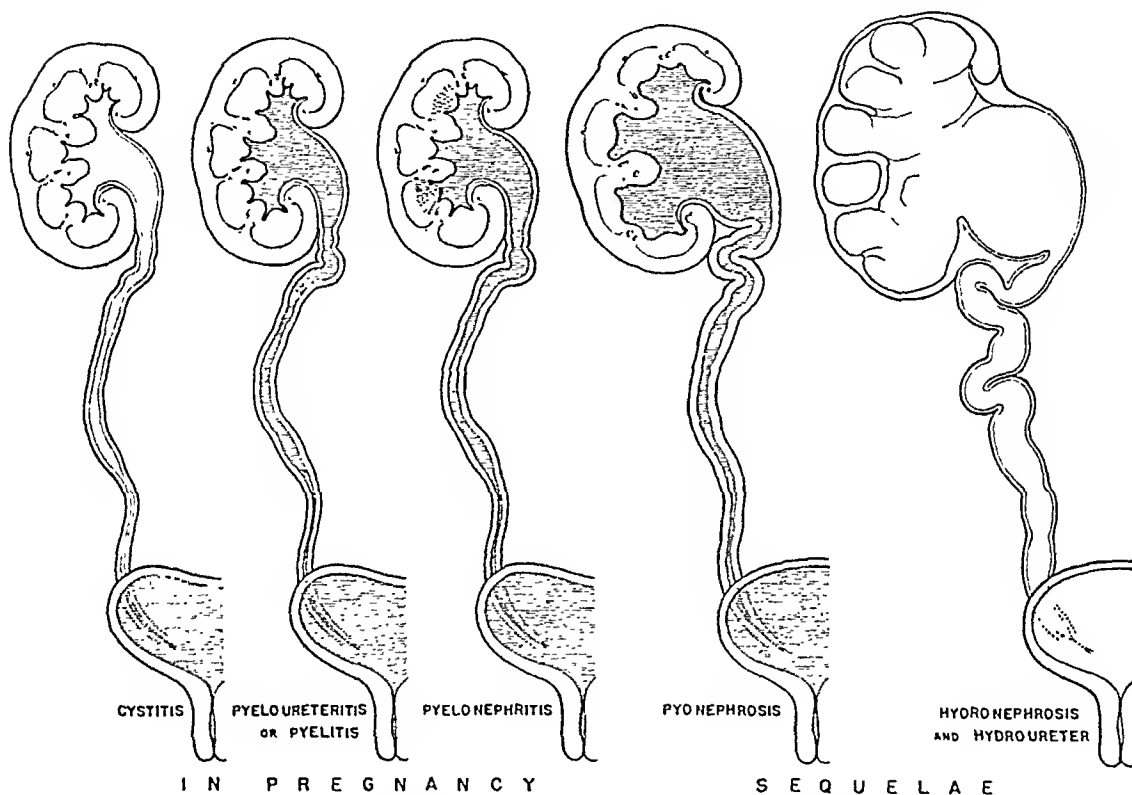


Fig. 1.—A diagrammatic demonstration of the portions of the urinary tract involved in the common types of infection complicating pregnancy and their sequelae in the puerperium. The shaded portions represent the extent of the infection.

health it may cause to mother and child. On the other hand, when adequately treated, the disease can be influenced to such a marked degree that most of its harmful effects can be obviated. It is, therefore, of primary importance that all obstetricians should have a clear understanding of the nature of the disease and its treatment.

ETIOLOGY

Three factors are of paramount importance in the etiology of pyeloureteritis of pregnancy. These are stasis, trauma, and infection.

Unfortunately a moderate degree of stasis of urine in the renal pelvis and ureter is a physiologic characteristic of pregnancy. In about 80

the colon group of bacilli. Occasionally we encounter streptococcus, staphylococcus, or proteus infections, but these are in the small minority. The fact that *B. coli* is the chief pathogenic invader suggests very strongly that this organism comes to the urinary tract from the bowel and that it does this either by direct ascent of the lumen of the tract or is transported there by way of the lymphatic system. The

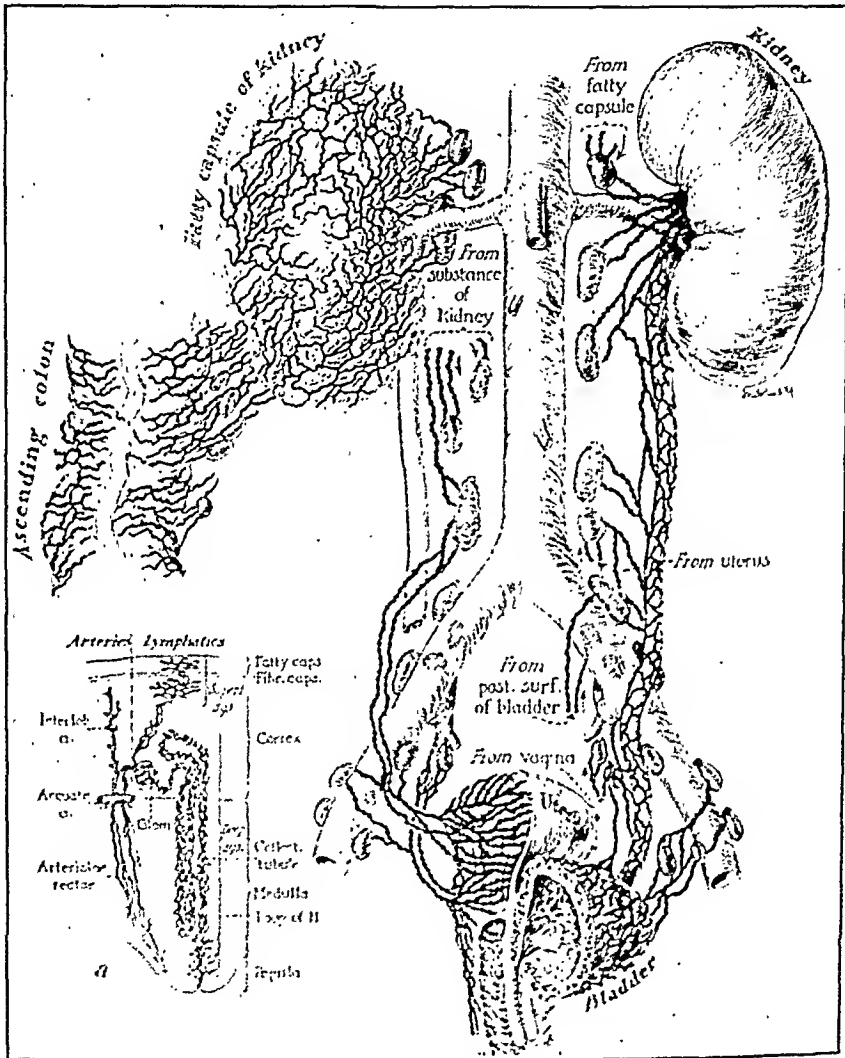


FIG. 4.—The various lymphatic pathways by which infectious organisms may reach the kidney and ureter from the large bowel and the pelvic organs. (H. A. Reimann.) (Permission of Lea & Febiger.)

older concepts of the mode of infection emphasized direct extension from the perineum to the urethra, thence to the bladder, and finally into the ureters and kidney pelvis (Fig. 3). This in times past has seemed a very reasonable hypothesis; however, most of the recent investigative work tends to indicate that this is not a common route. As Franke and others have shown, it now appears much more likely that in many instances the colon organisms are transmitted from the large bowel to

the right tract than in the left. This, it is thought, accounts in a large measure for the predominance of right-sided urinary infections in pregnancy.

The second etiologic factor of prime importance is infection, which results when a sufficient number of pathogenic microorganisms are introduced into the upper urinary tract to bring about inflammation.

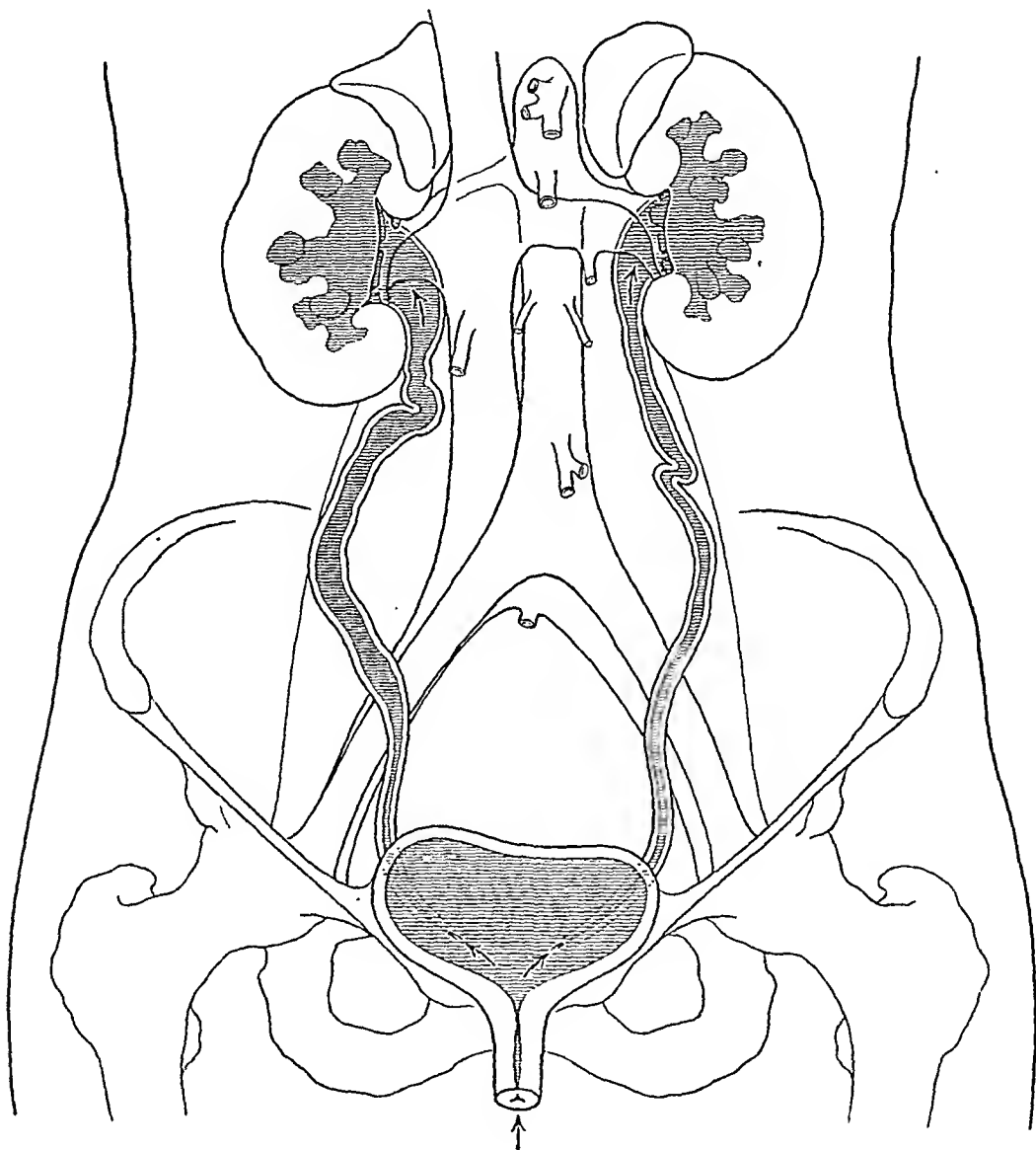


Fig. 3.—This picture shows the dilatation of the ureter and renal pelvis together with the lateral displacement and tortuosity of the ureter which comprise the characteristic changes in the tract due to pregnancy, the so-called physiologic hydroureter of pregnancy. The arrows and shaded portions demonstrate the "ascending infection" theory of the etiology of pyelitis, which is no longer accepted.

The phrase, "a sufficient number of microorganisms" has been used advisedly, for it has been demonstrated that a mild bacteriuria can exist without producing any considerable inflammatory reaction. It is noteworthy and probably very significant that over 95 per cent of the cases of pyelitis of pregnancy are caused by organisms belonging to

become so rigidly fixed in scar tissue as to render them incapable of peristaltic action, even after the inflammation has subsided. Thus the end-result may be a partially or completely inactive kidney pelvis and ureter, or if the process be continued longer, the woman may be left with a permanent pyo- or hydronephrosis. An appreciation of this sequence of pathologic developments impresses the necessity for the early employment of those therapeutic procedures which obviate or minimize them. Even with the best treatment we now know, we cannot completely stop the pathologic changes during pregnancy, for we have not yet learned how to rid the tract of infection while the uterus is distended by the fetus. Even though the patient becomes afebrile and the other symptoms subside, the urine cultures continue positive, as a rule, until some time after delivery, which means that a smouldering infection

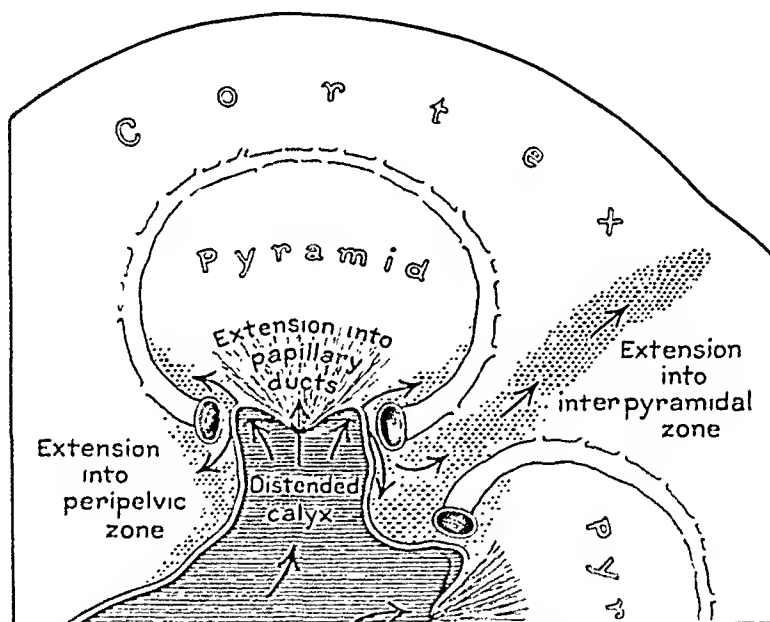


Fig. 5.—A demonstration of how infection may spread to the renal cortex from the kidney pelvis producing pyelonephritis by direct extension.

persists which, at any time, may cause a recrudescence of the acute aspects of the syndrome. The low grade infection of the tract progressively adds to the fibrosis of the ureters. However, this is small in amount as compared to the damage done during the acute exacerbations. Hence, a great deal can be accomplished by employing those forms of treatment which keep the reaction in a quiescent state.

The most serious form which the infection may assume is an extension upward from the renal pelvis into the glandular portions of the kidney, either by direct extension through the foramina papillaria or by extension into the peripelvic space and thence into the region of the interpyramidal septa (Fig. 5). Pyelonephritis is serious, either because it may markedly reduce the excretory function of the kidney or, because of its intimate relationship to an extensive vascular bed, it may produce such a

the capsule of the right kidney by the lymphatic system. This offers another explanation for the predominance of right-sided infections. Another very important route of infection also involving the lymph stream is that which drains the pelvic organs, particularly the cervix, vagina and urethra, and extends upward along the course of the ureter to the region of the renal pelvis where it empties into the lateral channels communicating directly with the thoracic duct. The studies of Winsbury-White have given such convincing proof of this lymphatic drainage that one is inclined to believe that this may be the most important of all routes of infection (Fig. 4).

Blood stream infection is in all probability secondary to that of the lymphatic system. In the majority of cases it would seem to play a minor part, despite the fact that there are competent observers who express themselves to the contrary.

The third etiologic factor is trauma. Scott has shown conclusively that the simple passage of a urethral catheter in the male may cause enough excoriation of the mucous membranes to permit large numbers of microorganisms to gain entrance to the blood stream and produce the well-known "catheter fever." Whether the bacteria reach the blood stream directly or by way of the lymph stream is a mooted point; the fact remains that slight trauma may cause the dissemination of the pathogenic organisms. Certainly the trauma of delivery together with the secondary atony of the ureter which occurs immediately after childbirth are the principal factors in causing postpartum pyelitis.

PATHOLOGY OF PYELOURETERITIS

In the acute phase of the disease the infectious agent, usually *B. coli* in one of its many forms, produces an inflammation of the internal aspects of the ureter and kidney pelvis, with swelling and edema accompanied by an outpouring of leucocytes to form an exudate on the surface mucosa. Flakes of the leucocytic exudate become detached, float in the urine, and thus produce the cloudy urine which, when observed under the microscope, is seen to contain the "clumped pus cells" so pathognomonic of pyeloureteritis.

Later the submucosa and muscular layers become involved with all the concomitants of an extensive inflammatory reaction. In the early stages of an acute attack the tissue response is largely made up of tissue fluids and leucocytes. However, when prolonged, the connective tissue elements appear and become organized into structures, which at first are loosely arranged, but later consolidate to form fibrosis. The longer the process is allowed to progress, the more its density is increased, with the result that the muscular portions of the ureter and kidney pelvis may

Usually the febrile phase of the disease is a short one when well treated, passing into a subacute condition after a period of four or five days. A remission may occur at any time, for as has been pointed out, the infection is rarely cured during pregnancy; it becomes quiescent but is an ever present source of danger.

The infection is found to involve the right tract in the great majority of patients. This is so true that should the infection seem to be on the left side, one should at once think of the possibility of a bilateral infection and take the steps necessary to determine whether or not this be true. The importance of bilateral infections as compared to those which are definitely unilateral cannot be overemphasized, because the hazard to the patient is not merely doubled, but, on the contrary, is increased many times.

TREATMENT

The treatment of pyeloureteritis should be varied according to several factors which must be taken into consideration before deciding upon the course to be followed. Is the patient in the early stages of pregnancy, or is she approximately at term? What has been her previous obstetrical and urological history? Is the infection unilateral or bilateral? Is there adequate renal function or has the infection already reduced excretory activity? These are a few of the more important questions that must be answered.

Generally speaking, the treatment of the disease falls into two general categories; the first, which applies to the vast majority of patients, may be considered conservative or palliative, and the second, radical.

The palliative treatment consists of rest in bed with frequent change of position which shifts the weight of the uterus from side to side, so that the ureters can be emptied more readily, thus improving drainage of the tract. Fluids are forced, a bland diet is prescribed and a mild saline purge administered every other day. Immediately upon admission, three laboratory procedures are carried out: (1) A catheterized bladder specimen is secured for examination and culture. (2) The blood is examined to discover whether or not there is nitrogen retention. (3) An intravenous x-ray pyelogram is made to furnish information as to the degree of damage already sustained by the inflammatory process and to serve as a rough test of kidney function.

If the organism is a colon bacillus, if there is no nonprotein nitrogen retention, and if the process is unilateral, the patient is carried on the palliative treatment for as long as seven days. Usually before that time has elapsed there will be a marked fall in temperature, and the kidney tenderness will be greatly diminished. In fact, most patients will respond to this treatment and go on to term satisfactorily. After the temperature has been normal for several days the patient is allowed to resume her activities in a modified manner, emphasis being placed upon

widespread infection as to endanger the life of the patient. It is quite probable that a slight degree of pyelonephritis occurs more frequently than is commonly thought, for it is very difficult to make a clinical differentiation between pyeloureteritis and pyelonephritis. Indeed, one cannot make a differential diagnosis until the inflammation has involved a considerable part of the kidney, so that its secretory activity is impaired and there is retention of nitrogenous substances in the blood stream. When the kidney is thus handicapped, one can easily come to the correct conclusion by examining the blood for nonprotein nitrogen constituents. When these are increased in amount, there is marked inflammation of the renal cortex, and when normal, there is little or no such extension. It goes without saying that a markedly elevated nonprotein nitrogen content of the blood indicates a very serious involvement of the kidney which demands vigorous and prompt measures if the patient is to be saved. More will be said concerning pyelonephritis when the treatment of the disease is considered.

CLINICAL FEATURES OF THE DISEASE

In our experience, pyeloureteritis occurs as frequently in multiparas as in primigravidas. The onset of the initial attack is usually in the last trimester of pregnancy or in the early puerperium. Not infrequently, however, we see women who, having had pyelitis in a previous pregnancy, afterward exhibit an exacerbation in the form of an acute reaction in the first or second trimester of a succeeding pregnancy.

The first symptom may be hematuria, although this is by no means constant. The acute phase is usually accompanied by a marked elevation of temperature, hectic type, and associated with chills. Anorexia, nausea and vomiting and some abdominal distention are frequently seen. There is usually pain, or at least demonstrable tenderness in the costo-vertebral angle corresponding to the side of the affected kidney. Upon inspiration, exquisite tenderness of the descending kidney may be elicited by deep palpation of the flank.

A catheterized specimen of bladder urine will usually show definite bacilluria and pyuria, the pus cells being clumped together, while bacteriologic culture of the specimen will reveal a strain of the colon family of organisms in the great majority of patients. Urine culture is important as staphylococcus, streptococcus, and *B. proteus* infections do not respond satisfactorily, as a rule, to the same treatment that is used for the colon organisms. Anemia is a frequent part of the picture because of the hemolytic propensities of many of the colon organisms. Blood cultures taken at the height of a chill are occasionally positive, indicating that the organisms have gained access to the blood stream. However, such cultures are much more commonly negative.

isms. The second employs mandelic acid salts which, when taken by mouth, are excreted in the urine and similarly are found toxic to colon organisms when the urine has a marked acidity. To produce the necessary urinary acidity necessitates some degree of acidosis on the part of the woman, the CO_2 combining power of the blood being depressed as low as 35 volumes per cent in some of our patients. Hence, these methods are probably not safe during pregnancy and should be confined to the puerperium until more is known concerning the actual danger their use may involve. It has also been considered unwise to allow nursing to continue during the course of this treatment.

TABLE I. MATERNAL MORTALITY—PYELOURETERITIS AND IMMEDIATE SEQUELAE

Sept. 1, 1932, to Sept. 30, 1936—New York Lying-In

I. Patients with pyeloureteritis	136
Patients with pyeloureteritis and excessive nonprotein nitrogen retention (above 50 mg. per cent)	16
	<hr/> 120

Therefore 120 may be assumed to have had simple pyeloureteritis and 16 pyelonephritis.

II. Deaths in the group of 120 cases of pyeloureteritis	0
Deaths in the group of 16 cases of pyelonephritis	4

Therefore the death rate is 25 per cent in pyelonephritis or 2.9 per cent in the whole group of upper urinary tract infections.

TABLE II. INFANTILE MORTALITY IN PYELOURETERITIS OF PREGNANCY

Sept. 1, 1932, to Sept. 30, 1936—New York Lying-In

Full term + premature infants alive	121
Stillborn + deadborn	11
Neonatal deaths	<hr/> 7
Total births	139
Incidence of infantile mortality associated with pyeloureteritis	12.949%
Incidence of infantile mortality from all causes	4.22 %
Infantile mortality is therefore increased three times normal experience	

The beta-oxybutyric acid bodies are induced in the urine by a ketogenic diet. This is an adequate diet in the sense that it provides a sufficient number of calories, but it contains such a high content of fat as compared to the carbohydrate component that incomplete oxidation occurs, ketosis results and the ketone bodies, chiefly beta-oxybutyric acid, are excreted in the urine. The treatment is efficacious if the urine can be kept sufficiently acid. This sometimes requires the administration of ammonium chloride if the urine is to reach the optimum acidity which is about pH₄. However, it is often difficult to gain the cooperation of the patient in carrying out this therapy, because the diet is a discouraging one to maintain. Another form of ketogenic diet based upon

frequent rest periods in the recumbent position during the day, and a continuation of an augmented fluid intake amounting to 3,000 c.c. per day. Close observation of the patient is maintained because of the danger of remission.

If, on the other hand, the patient does not respond to this conservative treatment after six or seven days of palliative therapy, the affected ureter is catheterized with a No. 7 or No. 9 catheter which is left in place with the tip high in the tract to provide drainage. The catheter is left in position not more than three or four days when it is removed whether or not the temperature and other symptoms have subsided. Frequently the desired response will come twenty-four or forty-eight hours after removal of the catheter. While the catheter is in position, lavage of the kidney pelvis with normal saline solution is carried out at four-hour intervals.

When the infection is bilateral, one is not justified in as long a period of palliation, particularly if the patient is two or three months from term. The possibility of pyelonephritis with suppression of function is so greatly increased that, if the patient does not respond promptly to palliative treatment or the use of the indwelling catheter, the uterus should be emptied. If, in addition to a well-established bilateral infection, one discovers nonprotein nitrogen retention, the termination of pregnancy should be mandatory. The danger of a fatal outcome for the mother is such a real possibility that delay should not be tolerated. At first this recommendation seems radical (Table I). However, when it is realized that once the renal cortex is extensively involved there is nothing the physician can do to influence the downward course of the disease, this attitude does not appear to be extreme. Furthermore, as the product of conception will very often be lost either through intrauterine death or abortion, it becomes even more evident that the evacuation of the uterus is not only a conservation procedure, but that it cannot be employed too early once the existence of extensive renal involvement has been established (Table II).

It is very gratifying to note the large proportion of patients who show a prompt remission of the more acute symptoms after the uterus has been emptied. This is to be explained by the release of pressure upon the ureters, cessation of back pressure upon the kidney pelves, and the improved drainage of the tract which follows.

The treatment of postpartum pyelitis either in the acute or subacute phase takes a very different form from that which has been outlined as applicable to the woman while the child is still in utero. In the puerperium we can safely apply the newer and more efficient methods of chemotherapy without danger. These take two general forms. The first and older method utilizes the principle that beta-oxybutyric acid in a markedly acid urine will quickly sterilize the urine of colon organ-

these appear, especially if accompanied by a fever or chill, the course of the disease can be minimized markedly by prompt institution of the palliative therapy which has been outlined.

In closing, it may be well to emphasize a few points which are essential in the treatment of the disease:

1. It should always be remembered that upper urinary tract infections are seldom eradicated during pregnancy when once there has been a sharp febrile reaction.

2. Pyelonephritis is a very serious complication which carries with it a definite mortality. Our only method of determining whether or not it is present is the chemical examination for excessive amounts of non-protein nitrogen in the blood. When the diagnosis is made, evacuation of the uterus is indicated.

3. Bilateral pyeloureteritis presents a very serious hazard to the expectant mother. If it does not yield promptly to conservative treatment, termination of the pregnancy should be seriously considered.

4. Postpartum treatment is necessary until such time as repeatedly negative urine cultures have been obtained.

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In the world literature are records of about 200 cases of rupture of the symphysis. Between 80 to 85 per cent of these were traumatic in origin and arose during operative deliveries. The remainder were spontaneous ruptures which occurred after spontaneous labors. Since, however, when the child is forced through the birth canal, considerable force is exerted in all directions, these ruptures also entail some degree of trauma. Hence a true spontaneous rupture of the symphysis is one in which there is neither external nor internal force. Hirsch reports such a case. The rupture occurred between the eighth and ninth months of pregnancy in a woman who did not have any trauma or pathologic bony process. The author believes the cause of the rupture was a pathologic degree of physiologic softening and relaxation of the symphysis. This in turn was due to a disturbance in the responsible gland of internal secretion.

J. P. GREENHILL.

the starvation principle has been more successful. With this a fairly well-balanced diet is possible, but an insufficient number of calories are given to maintain the body. In addition the carbohydrates are reduced. The effect of the diet is the same in producing the ketone bodies, but is associated with considerable weight loss. Of the two, the latter has been much the more successful in our hands, and has been most useful in combating deep-seated infection. However, both these ketogenic diets are being displaced in the treatment of pyelitis by the newer mandelic acid therapy.

Mandelic acid and ammonium chloride are combined to form an elixir which may be taken by mouth so that the patient receives in divided doses approximately 12 grams of the mandelic acid salt per day. Fluids must be limited to 1,500 c.c. or 50 ounces per day to prevent too great dilution of the mandelic acid salts in the urine. The therapy is not efficacious unless the urine can be maintained with a pH of 5.5. To control the latter, it is necessary to test the urine daily with an indicator such as methyl red, which changes color at a pH of 5.5. Occasionally an additional amount of ammonium chloride must be given to attain the desired degree of acidity, because patients vary markedly in response to the treatment. The mandelic acid treatment is given for a period of ten days; the urine is then cultured to determine whether or not the infection survives. If it does persist, the patient must be given a week's rest and then a new regime commenced repeating the same general precautions. A series of three negative urine cultures at weekly intervals are accepted as proof of a cure.

We are using the mandelic acid therapy in our postpartum patients and feel that it promises to give better results than the ketogenic diets because the patients are more cooperative in its use. We have not, however, applied it to the treatment of the antepartum patient because of the acidosis it produces. Its use is also confined almost entirely to patients with colon bacillus infections. Streptococci and staphylococci are little influenced by it. Proteus infections are resistant to this and any similar therapy which depends upon an acid urine, because this organism splits urea into ammonia which in turn alkalizes the urine and prevents the necessary degree of acidity being reached. Hence the necessity for knowing what organism is to be treated is quite obvious.

It would be a mistake not to point out the importance of antenatal prophylactic care in the prevention of pyeloureteritis and its sequelae. By encouraging all gravid women to drink copious amounts of fluids, at least three quarts a day, to rest in recumbent position for several short periods, as well as to carefully regulate the daily evacuation of the large bowel, much can be accomplished in reducing the incidence of the disease. In addition, the patient should be frequently questioned as to urinary symptoms, particularly hematuria and backache. When

In this study pH determinations are recorded. I am not sure of their significance. They might differ in untreated cases from the average range for normal adults of the same age group, since there is variation of the pH of the blood stream in pregnancy toward the alkaline side (Peters and Van Slyke). The normal range of pH for young adults is given by Peters and Van Slyke as pH 5.0 – 6.8 with a blood plasma pH of 7.4 which is a quite stationary figure. For want of a better setup the pH readings were made by means of the LaMotte indicator. For purposes of comparison pH 5.5 is selected as the division between acid and alkaline groups because it is at approximately this figure that bacteriostatic action due to acidity is supposed to begin. It is recognized that acidity alone is not bactericidal; yet our present knowledge of the constitution of the urine is not sufficient to enable us to deny the presence of normal antiseptic substances which are potent in acid urines. The basis of this statement is my observation that infections resulting from bladder or renal surgery which clear promptly and spontaneously are usually in strongly acid urines. It is also recognized that the type of infection in urine may influence it for greater acidity or alkalinity than is normal for that urine.

It is our practice at the Boston Lying-In Hospital, Out-Patient Department, to restudy infection cases which fail to clear by the end of the fourth month after delivery, with the purpose of determining the possible causes for persistence of infection. These causes may be found in the general condition of the patient; the renal condition; or the bladder condition.

The bladder is particularly conspicuous in this field because of the frequency of postpartum retentions and residuals. There is also the problem of bladder base injury which eventually results in cystocele formation. From the rarity of the finding of cystoceles in women of the child-bearing age in our clinic, and the eventual complete disappearance of bladder residual in most postpartum cases, even though bladder base injury is demonstrable, one must consider cystocele as a condition which is produced gradually after the injury occurs through loss of tissue resiliency and repeated functional stretchings of a weakened area.

Theoretically, retrogressive renal and ureteral changes begin immediately on delivery. In the majority of pregnant women they occur at a sufficiently rapid rate to give normal pyelography and a return of the pain reflex on distention through a ureteral catheter at the end of the fourth month, by which time the greatest numbers of recoveries from infection have taken place. In some instances, in spite of the absence of obstructive factors, this change is delayed much beyond this time limit. Where obstructive factors exist, not only does the retrogression

END-RESULTS OF URINARY TRACT INFECTIONS ASSOCIATED WITH PREGNANCY*

E. GRANVILLE CRABTREE, M.D., BOSTON, MASS.
IN COLLABORATION WITH DR. GEORGE C. PRATHER AND
DR. EDWIN L. PRIEN

(From the Urological Department of the Boston Lying-In Hospital)

END-RESULTS in urinary tract infections associated with pregnancy are, for the most part, rate of recovery from the infection, relation of such infection to subsequent pregnancies and the ultimate fate of the kidney. It was not always so. Infection of the urinary tract is capable of contributing to both maternal and fetal mortality in a large way. That it no longer does in the modern maternity clinic is due to better management which the last two decades of study of the problems concerned have made possible.

Present-day maternity clinics turn out four types of infection cases for aftercare. These are convalescing predelivery infections which have given no postpartum problems; second, infections involving the kidneys, which were not present during the pregnancy but took place during the puerperium; and third, cystitis cases without upper urinary tract involvement. These latter represent retentions and residuals following parturition where either intermittent catheterization or constant drainage has had to be employed and resulted in introduced infection. Fourth, pyelitis in pregnancy may also show pyelitis symptoms in the puerperium.

At the Boston Lying-In Hospital all such cases are directed to the Out-Patient Department clinic where they are followed until recovery takes place, a subsequent pregnancy intervenes, as all too frequently happens, or the case is restudied because of failure of the infection to clear.

Throughout all these studies of recently pregnant women one is impressed with the promptness as well as the completeness of cessation of all symptoms in prenatal infections on delivery, and the rarity of renal and cystitis symptoms in recently pregnant women. These factors added to ready disappearance of pus but persistence of bacteria lend a false security to the patient, mislead the obstetrician who relies on tests for albumin and pus without cultures or stained sediments, and falsify statistics. In these studies clearance of the urine of bacteria as demonstrated by sediments or cultures, or both, maintained over a period of one month without treatment, is the criterion for cure.

*Read (by invitation) before the New York Obstetrical Society, January 12, 1937.

Cystitis cases constitute the simplest field for study of infections as such, since the only possible complicating factors are the general condition of the patient and the presence of residual urine in the bladder, which is easily determinable. They have been purposely studied irrespective of the type of bacteria concerned in the infection. The results of observations on this group are shown in Tables I to III.



Fig. 2.—This excretory pyelogram shows extensive, and apparently permanent, bilateral, renal damage in a woman who has had eight pregnancies in ten years. The pyelography is remote from delivery (over one year). Pyelographic studies show no obstructive cause for hydronephrosis. Both kidneys have been explored surgically. No obstructive factor was demonstrated. Secondary small calculi situated in a calyx were present on the right.

TABLE I. RATE OF RECOVERY OF CYSTITIS CASES
68 CASES

WELL IN	1 MONTH	2 MONTHS	3 MONTHS	4 MONTHS	UNCURED
	38	20	3	2	5
Cases well in one month					
Without treatment	37 cases pH below 5.5 = 12.0 pH above 5.5 = 9.				
With treatment	1 case sent out of hospital on Hexamethylenamin.				
	38				

not occur above the point of obstruction, but through the lapse of time the condition progresses, because of further relaxation of the pelvic and ureteral musculature and the damaging effects of infection, an important item of which is probably mucosal edema and later chronic infiltration, which tend to increase obstruction (Fig. 1).

The presence of endocrine action as a factor in producing ureteral and pelvic dilatations in pregnancy is probable. If it occurs it probably appears early in pregnancy. Wilson and Abramson have shown that relaxation of the symphysis occurs in the first months of pregnancy. The occasional case is noted (see Fig. 2) in which, in the ab-

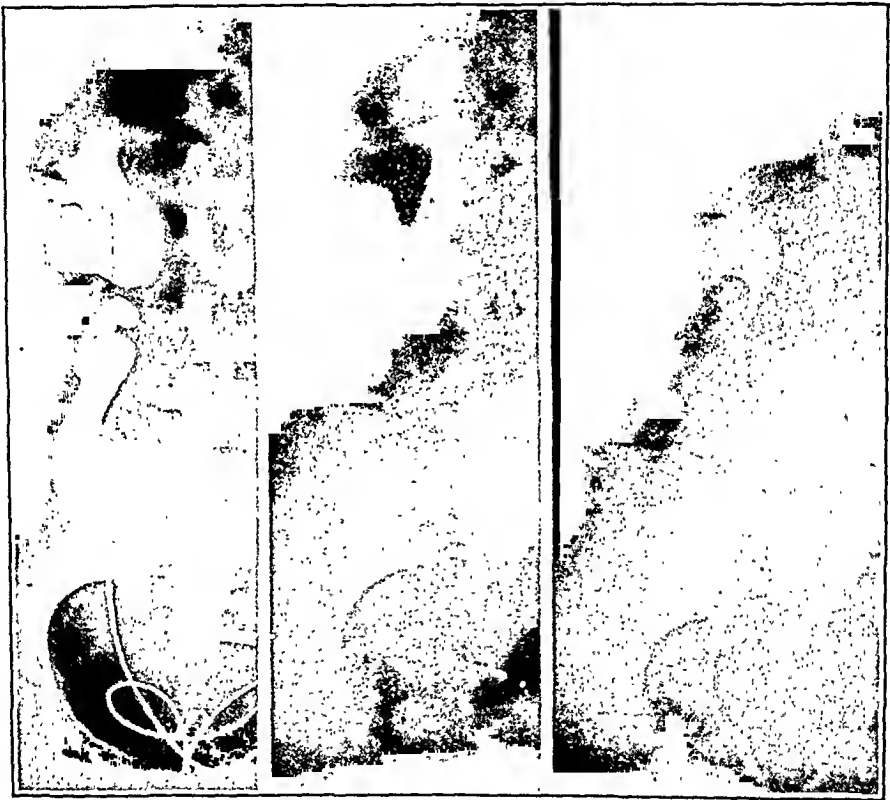


Fig. 1.—This series of pyelograms of the right kidney were made, reading from left to right, in December, 1935, April, 1936, and December, 1936. The patient was primiparous. Delivery was by cesarean section. There was neither bladder nor lower third of the ureter pathology. Birth canal injury was of course absent. Acute pyelitis in pregnancy was present but toleration for infection was acquired and the pregnancy completed. All pyelograms shown were made postdelivery. More than a year elapsed following delivery before retrogressive changes took place spontaneously and the infection recovered.

sence of either upper or lower urinary obstruction, marked degrees of dilatation of the ureters and pelvis persist which often become pyonephrotic. The obstetrical history is that of multiple pregnancies in rapid succession. Cases with a similar history but with pendant abdomens which would remove uterine pressure from the ureters have been found with minor degrees of dilatation but absence of the pain reflex on overdistention.

But 2 of these 9 patients had adequate pH readings for effective administration of formalin bearing drugs. All cleared up on acidification with formalin bearing drugs added. In view of the small number of patients who appear in the third group who recovered in three months without treatment, the need for treatment is not proved in spite of alkalinity of the urine.

In consideration of renal infections associated with pregnancy, cognizance should be taken of previous lines of thought, present expediency and completeness of investigation to include at this time what data I have concerning the significance of cured infections which existed historically previous to marriage and also of known infections which were present at the beginning of childbearing. The suitable cases at my command are limited in number. I will give them for what they are worth. These cases were studied in detail so that they might be safely used here.

TABLE V

Effect of Cured Preeexisting Urinary Tract Infection on Incidence of Pyelitis in First Pregnancy. Gross Pathology Excluded.

Old history of febrile urinary tract infection	1	
Pyelitis 9 years ago at Children's Hospital	1	
Pyelitis in infancy	<u>7</u>	9 total
None showed febrile pregnancies or infection		

While there were no urinary tract infections in this small group of studied cases, there is no reason why such cases should not participate in the normal incidence of infections associated with pregnancy.

Preeexisting uncured urinary tract infections without gross pathology: infections known to be present at inception of pregnancy.

2 Postmarital pyelitis and cystitis.
1 Pyelitis one year preceding marriage (cured in pregnancy).
1 Cloudy urine as a child, recurred 2 years before marriage.
1 Pyelitis 3 years preceding marriage.
<u>5</u> Total.

All five patients had pyelitis in pregnancy. One was cured in pregnancy. From this small group of cases, it is to be expected that in comparatively recent persistent infections there will be a febrile course to the initial pregnancy.

TABLE VI

Tolerance for Infection

109 infected pregnancies in 52 women. The infected pregnancy was not always the first pregnancy.

	Febrile	Afebrile
First infected pregnancy	48	3
Second infected pregnancy	23	26
Third infected pregnancy	<u>2</u>	<u>7</u>
	73	36 Total 109

In compiling these statistics no note was made as to whether infection was present previous to marriage to explain the occurrence of

Patients who were found to have recovered in two months after delivery consisted of two groups. The first group consisted of those patients who recovered without treatment of any kind, and the second group of those in whom some treatment was given.

Patients who recovered in two months without treatment were 11 of the 20 studied.

TABLE II

Patients not seen until two months, 8.	Patients seen but no treatment given, 3.
AVERAGE pH READING	AVERAGE pH READING
(1) 6.5	(1) 5.0
(2) 5.0	(2) 4.5
(3) 4.5	(3) No record
(4) 5.0	
(5) 7.0	
(6) 7.0	
(7) No record	
(8) 8.0	

It is possible that some of these patients had recovered before the date of their first visit to the clinic at the end of two months and may belong in the first group of one-month cases.

The pH readings seem to bear no relation to recovery rate.

Patients who recovered in two months with treatment given were 9 in number.

TABLE III

R Hexamethylenamin on spontaneous acidity—2 cases.	R Ammonium Chloride and Hexamethylenamin—7 cases.
(1) Average pH 5.0 (bladder residual ½ oz.)	Original pH Acidification
(2) pH 4.5, 6.0, 5.0.	(1) 6.0 4.5
	(2) 6.0 5.0, 4.5 Residual ½ oz.
	(3) 7.0 4.5, 5.0
	(4) No record 5.5, 4.5
	(5) 6.0 5.0, 4.5
	(6) 7.5 5.0, 5.0
	(7) 8.0 5.0, 5.0

TABLE IV

Patients who recovered in three months were but 3 in number.

	AVERAGE pH
(1) Not seen previous to the 3rd month	7.5
(2) Not well at one month, not seen subsequently until 3 months	5.0
(3) Known not to be well during 1st and 2nd months	4.5, 5.5, 4.5
There were no bladder residuals.	

Patients who recovered in four months were but 2 in number.

- (1) Untreated, not seen before fourth month. No pH recorded.
- (2) Treated with Hexamethylenamin on spontaneous pH 5.5, 5.0, 5.5, 5.0. There were no bladder residuals.

Five patients were uncured when last seen.

- (1) Bladder residual ½ ounces. pH reading—no record. Not seen after 1 month.
- (2) Bladder residual 2 ounces. pH reading—5. Not seen after 1 month.
- (3) Bladder residual 0 ounces. pH reading—5. Not seen after 1 month.
- (4) Bladder residual 0 ounces. pH reading—5. Not seen after 1 month.
- (5) The fifth case was returned to hospital in the first month for gross pathology.

Postpartum bladder residuals which persist much beyond discharge from hospital are not common. Data as to 10 cases observed show the following. These ten cases represent the total number of residuals found in 217 cases studied at the end of one month or longer after delivery.

TABLE IX

Pyelitis in pregnancy	
Cured	49% half in three months.
Chronic pyelitis	35%
Bacteriuria	16%
Postpartum pyelitis	
Cured	60%
Chronic pyelitis	10%
Bacteriuria	20%

TABLE X

$\frac{1}{2}$ OZ. RESIDUAL	1 OZ. RESIDUAL	1-2 OZ. RESIDUAL	$3\frac{3}{4}$ OZ. RESIDUAL
Well in 1 month 1		Uncured 1 mo. 1	
Well in 2 months $\frac{3}{4}$	Well in 3 mo. 3	Uncured 4 mo. $\frac{1}{2}$	Uncured 1 year $\frac{1}{1}$
	$\frac{3}{3}$		
	Total 10		

TABLE XI

1. No assignable cause found	1	
2. Neurosis, debility, negative urinary tract	1	} Debility
3. Anemia, debility	2	
4. Nephritis, debility	1	
5. Congenital strictures lower ends both ureters	1	} Anomalies
6. Double ureters with hydronephrosis	1	
7. Persistent pelvic and ureteral dilatations		} Effects of pregnancy
Right side only	2	
Bilateral	1	
8. Pyonephrosis		} Effects of pregnancy with anomalies or gross pathology
Diagnosed by surgery	2	
Diagnosed cystoscopically	2	
9. Bladder residual $3\frac{3}{4}$ ounces	1	Bladder
Total	$\frac{15}{15}$	

The findings in 15 renal cases which were returned for investigation for persistent infection beyond 4 months after delivery whether treated or untreated show the following causes for failure of recovery: Debility, renal anomalies, persistence of pregnancy changes, persistence of pregnancy changes with gross pathology or anomaly background progressing to pyonephrosis and bladder residual.

Table XII indicates that any persistent infection which either is present before pregnancy or persists between pregnancies may give *febrile* reactions during pregnancy. Forty-three cases studied.

Note that three cystitis cases gave febrile upper urinary tract symptomatology in the course of the next pregnancy.

Table XIII compiled from still another group of cases shows a majority of recurrent infections take place in the uncured cases. Forty-seven recurrent infections in subsequent pregnancies.

three afebrile first pregnancies. First infected pregnancies are quite decidedly more prone to have febrile reactions than subsequent ones. While no statistics can be given because of lack of complete pyelographic studies in all, there were instances in subsequent pregnancies where large pelvic and ureteral dilatation existed without fever's being shown at any time in the course of gestation. The figures justify the statement that the first of a series of infected pregnancies is more likely to show febrile symptomatology, but that due to acquired tolerance subsequent pregnancies, even though infection persists, are less likely to show pyelitis symptoms.

FATE OF UNCURED URINARY INFECTIONS IN SUBSEQUENT PREGNANCIES

In this study group are cystitis cases, pyelitis of pregnancy cases, and postpartum infections. A subsequent impregnation took place while infection was still present as shown by the bladder urine tests.

The first table indicates that if multiple infected pregnancies take place, irrespective of when in a series of pregnancies the first infected pregnancy occurs, infection can be expected to persist through subsequent pregnancies until cure between pregnancies can be accomplished. Naturally only women with several pregnancies could be selected for such a study (63 women).

TABLE VII

54	85.7% infected pregnancies (2-6 in number) were in sequence.
9	14.3% had one or more intervening uninfected pregnancies.
63	

Observers agree that persistence of the infection between pregnancies may be indicated by bacteriuria alone.

In consideration of the fact that there was not appreciable difference noted between the rate of recovery in pyelitis in pregnancy, postpartum pyelitis, and combined pyelitis in pregnancy with postpartum pyelitis, no separate listing is made and all are included under renal infections.

Rate of recovery in renal infections shows that 66 per cent of the cases are well in four months after delivery in untreated cases in a series of 44 cases studied:

TABLE VIII

	1 MONTH	2 MONTHS	3 MONTHS	4 MONTHS	TOTAL
Cured	8	11	6	4	29—66.0%
Last seen uncured	2	2	2	3	9—20.4%
Uncured at 4 months, returned for investigation					6—13.6%

The literature presents little end-result data. Dodds records the following data at the end of one year following delivery.

TABLE XIV

PARA	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	TOTAL
	3	4	1	4	1	0	0	1	1	0	0	1	16

The distribution of these cases numerically, according to the parity, is somewhat misleading since the number of women with completed pregnancies beyond 6 is not large. Miscarriages, due to whatever cause, were eliminated when considering the pregnancy infection as a pure bacilluria.

The three para i infections which remained bacillurias were in cases which were either of long standing, such as persistent pyelitis of infancy or were associated with chronic gross pathology also of years' duration.

THE FATE OF THE CHILD IN PYELITIS OF PREGNANCY

The pediatricians of the Boston Lying-In Hospital assure me that they cannot distinguish, by physical findings, a child born of a pyelitic mother from other infants. Unless premature these children equal the average in regard to nutrition, weight, and physical development. Likewise they are no more prone to anemias, feeding problems, or incidence of intercurrent disease.

It must not be forgotten that the acute phases of pyelitis, especially with dehydration, nausea, toxicity and consequent malnutrition, produce anemia very rapidly in pregnant women. Where the condition remains subacute with frequent exacerbations for several weeks or even months severe degrees of maternal anemia may result. Red cell counts as low as 1,500,000 with hemoglobin readings of 20 per cent have been noted in one patient whose physician placed her on a diet of orange juice and crackers over a febrile period of almost four months.

Minot, Straus, Castle, Rowland, Galloway, Wells, Talpade and others have studied both the nature of the anemias in pregnancy and the effect upon the child. They recognize four types of anemia.

TABLE XV

- Dilution anemia 60%-70% Hg. 3,000,000 red cell count.
- Pernicious anemia (the few pernicious anemia patients who become pregnant), red cell changes typical.
- A pernicious anemia of pregnancy 30% to 40%.
- Slow developing secondary anemia, variable in severity.

Dilution anemia is supposedly due to increased blood volume in pregnancy but the blood smear remains unchanged. It is, therefore, only a relative anemia. It needs no treatment.

The more profound type of rapidly developing "pernicious" anemia and the slower progressive anemia which show the blood picture of secondary anemia in various degrees of severity require treatment. Many pregnant women show hypochlorhydria. Castle has shown that these

TABLE XII

21	Infections following pyelitis during gestation.
10	Infections following postpartum pyelitis.
9	following preceding intercurrent infections.
4	pyelitis between pregnancies not due to the preceding pregnancy.
1	uncured for some years preceding pregnancy.
1	postmarital infection uncured.
3	cases with infected gross pathology (stones, etc.).
<u>9</u>	
3	cystitis cases without upper urinary tract infection.
<u>43</u>	

TABLE XIII

36	75.5% occurred in uncured cases
11	23.5% occurred in cases cured between pregnancies
<u>47</u>	Total
<i>The fate of cured cases after one or more infected pregnancy</i>	
89	cases studied
13	14.6% had pyelitis in pregnancy.

Vinay early called attention to the tendency of pyelitis to occur in subsequent pregnancies. Thirteen women of his group became re-infected.

Maujaka found 10 of 28 cases recurring.

Dodds' series showed 14 subsequent pregnancies, 3 of which were not yet at term, with four recurrences, 2 of which were hold-over infections.

Of Klaften's five subsequent pregnancies, 2 were uninfected, 2 had febrile pyelitis, 1 was a pure bacilluria.

There is an occurrence of infections in cured cases beyond the normal incidence of 1.5 per cent which is now coming to be accepted as the expected incidence for pyelitis in pregnancy in the general run of pregnant women. Several possible reasons can be suggested for this occurrence.

1. Failure of the pelves and ureters to undergo complete retrogressive change before the subsequent pregnancy. Stasis remaining is more likely to arrest and hold a bacterial invasion.

2. Failure to recover from the debility which the first infected pregnancy produced before the subsequent pregnancy.

3. Doubt as to the certainty of cure. I question that it is possible to determine certain cure within the time intervening between pregnancies in some cases.

BACILLURIAS DURING PREGNANCIES

Bacillurias in pregnancies without pyuria or pyelonephritis symptoms often accompanied by striking degrees of pelvis and ureteral dilatation seem to indicate that once tolerance for infection is acquired the pregnancy may proceed to completion with no other evidence of infection than the presence of bacteria in the urine. The following table illustrates the location of these bacillurias in respect to parity.

One hundred nine cases of multiple infected pregnancies, parity up to xii, showed 16 pregnancies in which the infection remained a symptomless bacilluria.

2. The majority of cystitis cases recover in the first month after delivery. The majority of renal infections clear within four months after delivery.

3. There is little difference in the rate of recovery among pyelitis in pregnancy, pyelitis in the puerperium and combined cases. They are best considered under the common heading "renal infection."

4. Renal infections which fail to clear within four months commonly do so because of four factors:

- a. Debility of the patient.
- b. Abnormal persistence of pregnancy renal changes.
- c. Abnormal persistence of pregnancy renal changes with anomalies or gross pathology.
- d. Bladder damage with residual urine.

5. A previous history of cured urinary tract infection without abnormalities of the urinary tract probably does not influence the incidence of pyelitis of pregnancy.

6. Infections which are uncured at the beginning of the first pregnancy probably produce febrile pregnancies in most cases.

7. Tolerance for infection either independent of pregnancy or associated with it seems to be acquired in many cases of long-standing infections. Such cases may be free from febrile symptoms during subsequent pregnancies or remain bacteriurias.

8. If multiple infected pregnancies occur in a series of pregnancies they are apt to be in sequence. The majority of recurrent infections in pregnancies take place in uncured cases but there is a higher incidence than normal in these "cured" cases.

9. Any form of urinary tract infection, even cystitis, may give rise to febrile pyelitis in subsequent pregnancy.

10. Infections which persist into the next pregnancy may remain symptomless bacteriurias, in spite of large renal and ureteral dilatations.

11. Residual bladder urines are not common in postdelivery cases, even though the injury from which cystocele eventually develops must be present. Cystocele, therefore, probably develops slowly following birth injury.

12. Small bladder residuals, under one ounce, seem not to retard spontaneous recovery from infection. Residuals above two ounces probably are of significance.

13. Children born of pyelitic mothers are not abnormal unless prematurity results from the severity of the infection.

14. Maternal anemia due to urinary tract infection or other causes may harm the child during its first year, although it is usually born with a normal hemoglobin.

15. Urinary tract infection as such is not transferred from mother to child as is congenital syphilis.

require both blood-building foods, such as beefsteak, and gastric juice in order to gain by diet alone. In these groups there is much evidence of dietary deficiencies. Treatment is by blood-building diet, iron, vitamin B, and liver extract. The action of vitamin B (yeast) and liver extract is inhibited by septic infection.

Straus indicates that in even severe untreated anemic mothers the child is born with normal hemoglobin, ranging about 100 per cent. After a few months the child falls into anemia during its first year. If the mother is adequately treated the child does not develop this anemia.

So far as infection is responsible for maternal anemia the child born of a pyelitic mother may suffer anemia during its first year, although born with a normal blood picture in spite of the degree of anemia which the mother may have.

In severe degrees of maternal urinary tract infection prematurity is the chief danger to the child. Tuberculosis of the kidney which has its inception during pregnancy is fortunately extremely rare. It accomplishes the complete destruction of the kidney or kidneys involved during the course of the pregnancy. When diagnosed immediate interruption is indicated. Pregnancy in chronic tuberculosis is not the same problem.

Diabetes together with pyelitis in pregnancy also rates interruption in our hospital. Occasional cases of virulent infections, especially where the organism is streptococcus, we also feel rate interruption. We recognize that intractable cases can be carried over to term if nephrostomy or pyelotomy is done. We hesitate to advise a procedure applicable to only a part of the childbearing life of a woman. The first renal operation is much easier to advise than subsequent ones since repeated operations on the kidney are both difficult technically, and endanger the integrity of the kidneys so treated. We prefer to interrupt intractable cases, cure infection, then re-engage in childbearing.

If the maternal anemia and infection of the urinary tract during pregnancy receive prompt recognition and modern treatment, loss of fetal life and prematurity will furnish but a negligible number of handicapped children in the wards of your hospital.

There is no indication, whatever, that the child participates in the mother's urinary tract infection similarly to congenital acquisition of syphilis.

CONCLUSIONS

1. Postdelivery urinary cases are of four types: Cystitis, pyelitis in pregnancy, pyelitis in the puerperium and those who have had pyelitis in pregnancy and also in the puerperium.

869 cases in the Obstetrical (ward) Service at the Woman's Hospital. In these 869 cases, there were 30 kidney infections, only 9 of which required ureteral catheterization.

As time has passed, I have had no reason to change my views upon this subject, and still feel that the same principles underlie the causation and treatment of kidney infections in the pregnant woman as in the nonpregnant, due allowance being made for the child.

DR. NATHANIEL P. RATHBUN.—Dr. Traut has made a distinction between pyeloureteritis and pyelonephritis. I am rather disposed to think that most of these cases are pyelonephritis and probably also ureteritis. I am not so sure that the blood chemistry index can be made the basis for differential diagnosis. It may be a criterion of the degree to which the kidney is infected, but I am of the opinion that all cases of pyeloureteritis are actually pyelonephritis as well.

In the matter of drainage there are several points about posture which are important. In the early months of pregnancy, when the uterus is riding on the pelvic brim, a little Trendelenburg posture is desirable, whereas in the later months of pregnancy the reverse of that, the Fowler position, is preferable. In many of these cases, particularly in the puerperium, but sometimes actually during pregnancy, there is a disturbance in the evacuation of the bladder. Some of these patients do rather well with an indwelling bladder catheter to keep the bladder empty. Dr. Crabtree remarked that he noted residual urine in comparatively few of these cases, but my experience has been that a good many of them have residual bladder urine.

During the febrile period, while I appreciate the fact that the colon bacillus is best attacked by various antiseptics effective in an acid medium, I am disposed to give these patients at first some form of alkaline diuretic. The urinary antiseptic for an acid medium can only be effective with a concentrated urine, and in these early cases we want to have a dilute urine, an alkalosis, and some form of diuretic to promote the flow of urine.

Another point of importance about the treatment of pyelitis during the puerperium is the necessity of complete and careful irrigation of the bladder and of the kidney pelvis. Sometimes it is desirable even in the acute cases to leave a catheter in the ureter, although I find occasionally that an indwelling ureteral catheter plugs the ureter rather than drains it.

DR. HENRY D. FURNISS.—I do not know whether we are justified in speaking of "the pyelitis of pregnancy," or whether we should term it "pyelitis and pregnancy." There have been a number of my patients with ureteral strictures who have subsequently become pregnant. I have predicted trouble for them and have seen my prophecies come true.

In pregnancy there is a normal dilatation of the ureter from hormonal action. With this normal dilatation plus a pathologic obstruction we have a combination which predisposes to infection. Kidd, in his book *Infections of the Kidney*, brought out the very illuminating observation that we are constantly absorbing into the blood stream bacteria from the intestinal tract. When well, and our resistance is good, the bacteria are normally killed off, but if anything occurs to lower this resistance we are very likely to be a prey to these bacteria. This may be brought about through overwork, mental strain, chilling, and intestinal derangement. In uncomplicated cystitis the factor of exposure to cold has been the greatest precipitating cause I have found.

The fetus is affected adversely in many of these cases, and while not apparent at the time of birth, these children are later found to be sub-standard, sometimes for a year or more.

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DISCUSSION ON PAPERS OF DRS. TRAUT AND CRABTREE

DR. HENRY G. BUGBEE.—The clinical picture in these cases, as I saw them in 1911 as urologist to the New York Lying-In Hospital, was characteristic. There was often an early history of a chill, followed by fever, perhaps with nausea and vomiting, always with abdominal distention, pain, and tenderness in the costovertebral angle. During this stage, urinary symptoms were rarely present, and the urine was often free of pus or contained only isolated cells, while bacteria were commonly found on smear or culture. As the bacteria were almost invariably colon bacilli, the first indication seemed to be a thorough clearing out of the intestinal tract, followed by colon irrigations with forcing of fluids to increase kidney elimination.

With the establishment of kidney drainage, costovertebral tenderness invariably subsided and bladder symptoms (dysuria) supervened, the urine then showing quantities of pus and large numbers of bacteria. If kidney drainage did not take place at once, ureteral catheters were passed and retained if necessary. When the catheters were passed unmistakable signs of retention of urine beyond a point of ureteral occlusion were almost invariably present, the occlusion being most often in the lower ureter on the right side.

Urinary antiseptics were then found to be efficacious, and with the subsidence of the acute infection, every effort was made through forced elimination, intestinal and urinary, to carry the patient through the pregnancy. The knee-chest position for certain periods of the day was found beneficial, and after delivery a study of the urinary tract was carried out to ascertain the possible existence of an underlying urologic lesion.

As time passed, I was called upon less frequently to see these cases, as the prophylactic care which was instituted by the members of the staff was efficacious in preventing many infections. In other instances, the infections were so much less severe that they responded readily to routine medical treatment.

A great variety of underlying lesions of the urinary tract was found, over a period of twenty-three years, consisting of the following anomalies: pressure upon the kidneys or ureters, causing displacements and narrowing of the lumen of the ureters; constrictions secondary to anomalous vessels; strictures of the ureters; the presence of a tumor of the urinary tract; calculi; even polycystic and ectopic kidneys. All of these gave impaired urinary drainage and thus predisposed to infection. Focal infections in various parts of the body were often discovered and eliminated. Yet in a large proportion of cases, pressure upon the ureter by the uterus, with atony of the ureter and the kidney pelvis, was the only anatomic lesion present. The same observations have been made in the service at the Woman's Hospital over a corresponding period. During the past year there were

A STUDY OF THE END-RESULTS OF THE TREATMENT OF
AMENORRHEA AND STERILITY BY RADIATION
OF 128 MARRIED WOMEN OVER A PERIOD
OF TWELVE YEARS*

IRA I. KAPLAN, B.Se., M.D., NEW YORK, N. Y.

(Director of the Division of Cancer, Municipal Department of Hospitals)

EIGHT years ago, and again in 1931, we¹ reported on our treatment of a limited number of cases of amenorrhea and sterility with x-ray therapy. Now, after observing a larger number of patients and their children over an extended period of time, in some instances ten years, we are still of the opinion that in no other field of gynecology is irradiation more helpful and promising than in the treatment of functional disturbances of the ovary and in sterility.

Unfortunately, there still exists among the profession a definite prejudice against irradiation for therapeutic purposes, based upon misconceptions or hearsay evidence of harmful effects upon both mother and offspring which are uncontrollable. Such misconceptions were recently stressed by a committee of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons,² who have added instances of ill effects on the offspring, totally disregarding the successful results obtained by careful workers. There is no question that irradiation during pregnancy is in many instances harmful to the unborn child, the harm depending to a great extent on the age of the embryo and the amount of irradiation given. Nevertheless perfectly healthy children have been born to mothers who were irradiated for malignant conditions during the course of pregnancy.

We reported such a case in 1930,³ and Neill⁴ recently reported a fortunate outcome in some of his cases, citing several instances reported by others. In 1926 Rubin⁵ reported successful results in the treatment of patients with amenorrhea and sterility. Though his series was small it demonstrated that x-ray therapy had an appreciable therapeutic effect when applied to the pelvis and pituitary.

Further study of successful results in a larger group of cases with subsequent follow-up of children born of irradiated mothers, leads us to reiterate our previous conclusions that irradiation when properly given is neither harmful to the mother nor to the offspring and has proved a valuable therapeutic procedure for the treatment of amenor-

*Presented, by invitation, before the New York Obstetrical Society, December 1, 1936.

In mandelic acid therapy we have something of value in urinary tract infections. Frequent urinalyses are necessary during the administration of the drug as many develop albuminuria and casts. I have not, however, observed the development of acidosis when this drug is used, even in pregnancy.

DR. TRAUT (closing).—I would like to clarify my use of the term pyelonephritis and am very grateful to Dr. Rathbun for pointing out what is apparently a misunderstanding.

Pyeloureteritis and pyelonephritis are clinical-pathologic terms representing the extent of involvement of a disease process. They can be used quite accurately by the pathologist, as he can examine the organs and observe the products of inflammation. For the clinician to use them correctly is a much more difficult matter and yet, as has been pointed out, it is very important for him to do so, as the first is a relatively benign process associated with no mortality, whereas the latter is an extremely dangerous complication.

The only means available for a clinical diagnosis between pyeloureteritis and pyelonephritis is the use of the nonprotein nitrogen or urea nitrogen estimation of the blood. I hoped that I had made it clear that even this test gives us the correct diagnosis only when a considerable amount of kidney damage has taken place and that its warnings are therefore very important ones indicating prompt action if the patient is to be saved. I must re-emphasize this point, for it represents the most important advance that has been made recently in the treatment of the acute phase while the fetus is still in utero.

Whether there is or is not some degree of parenchymal involvement of the kidney in every case of pyeloureteritis in pregnancy is, for the moment, of academic importance only because the opinions of authorities differ markedly. We can say, however, with certainty that in pyeloureteritis with no retention of nonprotein nitrogen in the blood stream we are dealing with a process which has not caused damage to the excretory organs of such a nature as to cause death, whereas, when nonprotein nitrogen retention occurs, grave alterations have taken place, which we choose to characterize, rightly or wrongly, as pyelonephritis and which we have learned are associated with a high mortality (25 per cent).

With the increased use of this test in pyeloureteritis of pregnancy much will be learned concerning kidney involvement on the one hand, and on the other, lives will certainly be saved if its warnings are heeded and the burdens of pregnancy promptly removed and adequate drainage established.

DR. CRABTREE (closing).—I want to make myself clear on one point. I do not deny the existence of postpartum bladder retention and residual urine while the patient is in the hospital. I am calling attention to the fact that in this series of 217 cases seen at least a month after delivery there were but 10 instances in which there was residual urine shown on repeated examination.

Barsony, Eugenio: Endometriosis of the Uterine Adnexa, *Monitore ostetrico-ginecologico* 8: 375, 1936.

The author after discussing the symptomatology of tubal endometriosis describes four cases of adnexal endometriosis. He analyzes the mechanism of the rupture of the adnexal sacs. On account of the resulting peritoneal irritation and internal hemorrhage, adnexal endometriosis is clinically often mistaken for extrauterine pregnancy.

AUGUST F. DARO.

other surgical corrective measures were carried out. Of the 128 patients treated 43 were treated for amenorrhea varying from months to years, 41 for amenorrhea and sterility, 11 for sterility alone, and 33 for oligomenorrhea, the menstrual intervals being several months.

TREATMENT

X-ray Therapy.—In all instances treatment consisted of x-ray irradiation to the ovaries. In 80 cases an additional treatment was given to the pituitary and in 5 instances also to the thyroid. The factors used were: 200 K.V., 4 M.A., with the filter of 0.5 mm. copper and 1 mm. aluminum, at a target distance of 30 to 40 cm. Treatment was directed through 4 pelvic fields, 9 by 12, 10 by 15 cm., and to the pituitary area of 6 by 8 cm. The dose given was 75-150 r. units (measured in air) per field at intervals, one treatment per week for three weeks. Occasionally a fourth treatment was administered.

Results.—Of the 76 patients whose menstruation was reestablished, 44 patients became pregnant. In 84 instances no pregnancy occurred. Of the 44 patients who conceived, 2 are at present in the course of their pregnancy, 17 have conceived more than once, 5 conceived but aborted, 2 of these aborted twice. Thirty-six patients became pregnant and went to term, giving birth to 47 living children and one stillbirth with an abnormal fetus. Nine women have had more than one child. There was one case of twins. Of the 44 pregnant patients, amenorrhea existed from one month to fourteen years, and sterility from one to eighteen years. Only 4 patients had previously borne children, 3 had previously aborted or miscarried.

None of the patients treated were harmed in any way. In no case did menstruation cease or become scanty where menstruation had previously occurred in the usual manner.

The 36 women who bore children had amenorrhea and sterility as seen in Table I. All these patients received x-ray therapy to the pelvis and 18 received additional treatment to the pituitary. In 2 cases the thyroid was also treated.

A study of the surviving children shows them all to be normal, both physically and mentally. Reports from the parents have in no instance disclosed any abnormality, nor any physical deformities. There are 25 boys and 22 girls in this group, the oldest under study is now ten and one-half years of age. Photographs of many of these children are attached.

Abstract case histories of the 44 pregnant patients are reported.*

Now, as to the explanation of the action of the x-rays. Although in 1905 Halberstaedter⁶ first demonstrated the selective action of x-rays on the ovaries, still the reaction to x-rays are not as yet clearly under-

*For lack of space the abstract case histories will appear in the author's reprint only.

rhea and the relief of sterility. In a recent report by Mazer and Spitz⁶ who obtained 50 per cent pregnancies in their cases, they have arrived at the same conclusion.

In our series we have had but one untoward effect, reported in 1932.⁷ In this case treatment was administered when there already existed an embryo in utero, which is quite another matter than the subject under present discussion. The effect of x-rays upon the embryo is profoundly different from the effect upon unimpregnated ova.

The reason for again calling attention to this mode of therapy is warranted because no other treatment so far devised, including organotherapy, has yielded satisfactory or equally good results. The enthusiasm aroused by endocrine studies in this direction has so far led to disappointment. Stein and Leventhal⁸ have shown that endocrine therapy is of no avail in cases of cystic ovaries, amenorrhea and sterility. Many of our patients received irradiation only after prolonged endocrine therapy had proved unavailing. One case in particular, a young woman of twenty-seven years had submitted to two years of persistent endocrinologic investigation and hypodermic injections. Her arms and legs had been treated like pineushions. She accepted x-ray therapy as a last resort which the result has fully justified. Having menstruated at monthly intervals for four months following the x-ray treatment, this patient is at present in the eighth month of pregnancy.

Our present report is based upon a study of 128 married women who were referred to us in private practice during the period of 1924 to 1936 for treatment of amenorrhea and sterility. An appreciable number of cases of single women treated by us for amenorrhea are not considered in this study. We have follow-up records in 114 patients. Whether or not some of the 14 who could not be traced may have responded to the treatment, they are regarded by us in this study as failures. The menses were regulated in 76 women and in 52 there was no improvement.

The oldest patient treated was forty-five years of age, the youngest nineteen. The ages in the successful group varied between twenty-one and twenty-nine years in 46 patients, and between thirty and forty-five years in 30 patients. In the unsuccessful group 25 patients were between twenty-four and twenty-nine years of age, and 27 between thirty and forty-five. We noted that the younger the patient the more amenable to treatment.

In all instances some form of endocrine therapy, including tablets of ovarian substances and the newer hormonal substances, had been used and proved unavailing. All the cases had previously been examined for gynecological abnormalities. In many histories previous tubal insufflation was recorded, and in a number of instances the husband had been examined for potency. In 8 cases previous curettage or

his coworkers have definitely demonstrated that the pituitary is indispensable for menstrual bleeding to occur. Lacassagne¹¹ states that only one-third of the anterior lobe of the pituitary is sufficient to preserve genital activity and that a definite minimum of anterior lobe is required to maintain normal physiologic balance of ovarian function.

At the present time we are inclined to attach prime importance to the pituitary as the factor controlling menstrual function. Do the x-rays to the ovaries activate that "bleeding factor" of the anterior pituitary which then produces menstrual bleeding, as suggested by Wilson and Kurzrok?¹² It is evident that normal genital function of the female depends upon the proper correlation between the pituitary, the ovary, and the uterus.

Aschheim and Zondek¹³ proved that the pituitary produces its effect only when the ovary is present. Allen¹⁴ states that the anterior pituitary controls and maintains the action of the ovaries, and Novak¹⁵ ascribes this control to the gonadotropic hormones produced by the basophile cells.

Beclere¹⁶ was the first to report the effect of x-ray on the pituitary. Lacassagne¹¹ has shown that the anterior lobe of the pituitary is most resistant to destructive effects of irradiation and therefore therapeutic irradiation of the pituitary is not harmful. Werner¹⁷ found that x-ray treatment of the pituitary stimulated menstrual reaction, and because of this so-called stimulating action Borak¹⁸ suggested pituitary irradiation for mitigating climacteric symptoms of early menopause.

Frank¹⁹ states that in the normal mature fertile woman the ovary secretes two hormones, the estrogenic factor and the progestational factor, and that normal genital function is dependent on the synchronism of prepituitary estrogenic and progestational blood cycles. Mazer agrees with Frank that the normal menstrual cycle depends upon the balanced activity of the two ovarian hormones. Mazer and Andrussier²⁰ emphasize the definite dependence of ovarian function upon hormonal stimulation from the pituitary. Corner²¹ states that progestin, the hormone of the corpus luteum, will help cases of sterility and habitual abortion, due to lack of corpus luteum, as it acts as a menstruation suppressor. Allen says experiments have shown that surgical removal of the corpus lutea brings on menstruation. Cystic conditions of the ovaries may readily produce amenorrhea or sterility and, as Stein and Leventhal have shown, endocrine therapy is of little avail in such conditions, mechanical means constituting the only procedure for relieving the condition.

Although x-ray treatment of the pituitary appears to be efficacious it does not account for the favorable results in all our patients, as only 18 received this treatment.

Does x-ray act mechanically, as in the case of polycystic ovaries which are relieved (Stein and Leventhal) by mechanical destruction of the cysts? In our series, one patient had cystic ovaries, proved at operation. Sterility was relieved by x-ray therapy. Perhaps by destruction of the cysts? Does it destroy the corpus luteum which suppresses menstruation according to Corner, or does it stimulate general endocrinologic action and reaction in the body, setting in motion the

stood and their biologic action on the ovary not entirely elucidated. We are not yet definitely clear as to the real cause of menstrual bleeding, although recent endocrinologic studies have shown an undoubted relationship between the ovary and the pituitary. This interrelationship has been recognized for many years but recently Hartman¹⁰ and

TABLE I

NAME	AGE	YEARS OF STERILITY	PREVIOUS CHILDREN	PREVIOUSLY MISCARRIED	AMENORRHEA	PREVIOUS OPERATIONS
R.	28	6	0	0	Irreg. 1-3 mo.	0
A.	28	4½	0	0	6	0
A.	28	2	0	0	1	0
B.	27	3	0	0	6-8 mo. scanty	1 curettage
B.	24	4	0	Feb. 1926	7 mo.	1 curettage
B.	22	1	0	Aug. 1924	3 mo.	0
B.	24	4	0	0	3 mo.	0
C.	30	8	1 still-birth	0	Irreg. 1 mo.	0
C.	26	6	0	0	Irreg. 1 mo.	0
C.	26	5	0	0	13 mo.	0
D.	32	3 (14 yr. married)	3 (youngest 6 yr.)	0	Irreg. 3-6 mo.	0
E.	24	3	0	0	12 mo.	0
E.	29	7	1 (6 yr. old)	0	5 mo.	Cervix cauterized
F.	29	3	0	0	Irreg. 2 mo.	0
F.	28	3	0	0	13 mo.	0
G.	21	1	0	0	Irreg. 3 mo.	0
G.	27	3	0	0	Irreg. 3 mo.	0
G.	34	4	0	0	Irreg. scanty	Oper. infantile uterus cystic ovary
G.	30	3	0	1924	8 mo.	Curettage
J.	30	5	0	0	14 yr.	0
K.	31	2	0	0	Irreg. 3 mo.	0
L.	22	2	0	0	Irreg. 5-8 mo.	0
L.	25	3	0	0	Irreg. 5-6 mo.	Curettage
M.	21	3	0	0	11 mo.	0
M.	23	3	0	0	5 mo.	0
M.	25	4	0	0	Irreg. 2 mo.	0
M.*	21	Not married	0	0	Irreg. 3 mo.	0
M.	34	3	0	0	Regular	0
O.	30	6	1 still-birth	0	Irreg. 2 mo.	Electric
R.	22	3	0	0	Irreg. 1 mo.	0
S.	24	5	0	0	3 mo.	0
S.	24	2	0	0	3 mo.	0
S.	33	17	0	0	Irreg. 1-4 mo.	Curettage
S.	31	8	0	0	12 mo.	0
U.	28	8	0	0	Irreg. 3 mo.	0
A.	28	4½	0	0	Irreg. 6 mo.	Curettage

*When first treated.

The treatment must, as Mazer has emphasized, be given with care and in suitable cases.

SUMMARY AND CONCLUSIONS

X-ray therapy is of definite value in the treatment of functional disturbances of the ovary and in sterility. Irradiation is applied to the pelvis in most instances, and in some cases to the pituitary as well. Whether to treat only one or both is a matter of judgment, based on training and experience.

Careful observation over a number of years of children born of mothers so irradiated shows that such children are in no wise abnormal physically or mentally.

Detailed case reports are included in the author's reprints. They are omitted here for lack of space.

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DISCUSSION

DR. WILLIAM P. HEALY.—A communication of this kind requires serious consideration from us, because it represents observations over a period of years of a large series of cases. The literature is moreover being added to daily, indicating that there is value in this method for the treatment of amenorrhea and sterility.

Dr. Kaplan's small series of 11 cases treated for sterility only are, I assume, those patients who had a normal menstrual function. I wonder upon just what theory he expects to get a result from the treatment of these, and in what percentage a favorable result was actually obtained. I would be interested in knowing also how soon the average patient responds to the treatment for amenorrhea, and how much time Dr. Kaplan would allow before saying that the treatment was ineffectual.

The question of sterility is a different matter. Were it not for the fact that in many of these cases the patients had been treated for a long time for their sterility without avail previous to the use of the roentgen therapy, one would be inclined to say that the relationship of the conception to the therapy was unproved. Sterility is so easily and so effectually overcome by many different procedures. I think, however, we must agree that these cases represent successes achieved in instances of failure by other methods of treatment.

normal interchange of hormones which produce normal pituitary, ovarian and uterine function and thus allow for menstruation and subsequent pregnancy?

Hutton²² and his coworkers in their study of the action of x-rays on the mechanism of blood pressure control have definitely shown that x-rays have an appreciable effect on the endocrine system. In our own observations²³ we have noted that irradiation of the ovaries in castration doses inhibited epileptic attacks which accompanied normal menstruation suggesting some relationship to the brain. The effect upon the rest of the endocrine system if applied to the ovaries may also be assumed to be reciprocal.

Wilson and Kurzrok¹² state that actual bleeding occurs only if the bleeding hormone is not inhibited by the corpus luteum hormone. Does the x-ray destroy this inhibitory function of the corpus luteum? In our series in which 44 patients became pregnant following x-ray treatment, 7 cases had previous pregnancies, 4 of whom bore normal children, and 3 miscarried. Perhaps these had a persistent corpus luteum which inhibited menstruation and caused subsequent sterility. X-ray therapy by destroying the corpus luteum permitted these patients to menstruate, conceive and deliver normal children. Mazer and Andrussier state that organotherapy is far less effective than irradiation of the affected endocrine glands in the successful reestablishment of menstrual periodicity. Taylor²⁴ likewise has shown that organotherapy is of little value in controlling mastitis associated with menstrual disorders and states that x-ray therapy is often of definite therapeutic value in this condition, the x-rays achieving the result through the endocrine system.

Wolf,²⁵ investigating endometrial biopsies obtained from cases of amenorrhea, states that the symptoms may be the result of:

1. Absence of function of the anterior pituitary lobe where the gonadotrophic hormones originate. The endometrium is atrophic
2. Excessive amount of follicle-stimulating hormone, producing single or multiple granulosa cysts in the ovary without corpus luteum formation. The endometrium is hyperplastic (polyhormonal amenorrhea of Zondek).
3. Excess of luteinizing gonadotrophic hormone which results in a persistent cystic corpus luteum of the ovary. The endometrium is in the premenstrual phase.

In Wolf's opinion x-ray therapy directed to the pelvis is of no avail in Group 1, yet we have very numerous instances of apparent stimulation of pituitary function in this group. In Group 2 the x-ray, he states, destroys the persistent follicle, resulting in anovulatory bleeding and the results are generally good. In the third group, x-ray, by destroying the persistent corpus luteum, causes bleeding from a premenstrual endometrium. In our work with the treatment of neoplasms, we have had frequent examples of actual tissue destruction by x-rays and can readily conceive of such a result on the follicle cysts.

Whether the x-ray affects directly the ovary, the uterus, or the pituitary, or is an indefinite endocrinologic factor stimulant, may be debated. Despite this the fact remains that it has been a definite factor in the successful treatment of the cases herein reported.

patient may be. If you irradiate a woman who has had her period six, seven, or eight weeks ago, although she menstruates habitually every four or five months, you may strike an early period of gestation. The Aschheim-Zondek test in such instance can exclude the possibility of pregnancy.

The results promised from endocrine therapy made me, among others, abandon the radiation treatment for the time being, although I had had very good results up to 1929. Since that time I have used x-ray treatment in a few cases because hormonal therapy has proved ineffectual in this particular group. Experience has proved that the amenorrhea associated with sterility once being corrected is then followed by pregnancy in an appreciable number of cases.

The difference between x-ray therapy and the more effective hormonal substances such as progestin and proluton is also of interest. There is no doubt that the menses may be induced by such hormonal therapy once, and even twice, and in an occasional case regular periods may follow. The x-rays induce menstruation which becomes regular in the vast majority of the amenorrhea cases so treated. There is no doubt that if we could obtain effective hormonal substances to correct deficiencies in function which we could definitely diagnose that then we should have reached the ideal in therapy, for the fear is still entertained by many that x-rays have a deleterious effect upon the germ plasm. In the children so far observed born of mothers who received x-ray treatment in fractional doses I have personally not observed any signs of degeneration which confirm the observations of Dr. Kaplan. However, there is still the theoretical possibility that a third or fourth generation may exhibit stigmas traceable to such treatment. Until this is proved and until endocrine therapy accomplishes more regular and dependable results, we may well consider recommending this form of radiotherapy in properly selected cases.

DR. SAMUEL H. GEIST.—Aside from the study of the effect of the x-ray on the ovarian structure, the hormone response may also be a subject worthy of study. In the first place, what is the hormonal disturbance associated with the instances of amenorrhea and sterility? Is there a diminution or absence of the estrogenic factor or is it a gonadotropic factor which is deficient? Information of this character would possibly indicate which gland should be treated, if any.

Pituitary radiation, at least in the one case, which I had the opportunity of examining, failed to affect the histologic structure of the pituitary. This patient had received a tremendous dosage for a presumable basophilic adenoma. Of course, it is possible that physiologic activity may be disturbed without a change in the physical character of the cells. X-ray of the pituitary has been employed to relieve menopausal symptoms which are presumably due to a hypersecretion of the gonadotropic hormone. In Dr. Kaplan's case, on the other hand, x-ray of the pituitary was instituted to increase the amount of gonadotropic hormone. However, from the report tonight of 44 cases of sterility and amenorrhea of long duration successfully treated, we can assume that there is some causal relationship between the radiation and the result.

DR. JAMES A. CORSCADEN.—While it is true that an early embryo after x-ray may develop into a normal individual, something over 60 per cent will be born with mental defects. We should all be very cautious therefore about radiating any woman with an early embryo.

I suppose some statistical expert might somewhat reduce the percentage of successes reported by Dr. Kaplan, but I think from the standpoint of ordinary common sense, we must accept this as a contribution of fact.

In regard to the speculations concerning the mechanism, of the action of x-ray in these cases, the theory that seems to me most attractive is that directed toward

DR. HOWARD C. TAYLOR, JR.—The evidence which Dr. Kaplan brings, that x-ray stimulates or regulates the ovarian function, requires a consideration of the mechanism by which this is brought about. First, the x-ray may act directly to stimulate the granulosa cells, an effect difficult to prove. Second, the x-rays may be effective indirectly, through the blood vessels in the production of an hyperemia, that itself improves the nutrition of the ovary. Third, it is possible that the x-ray has a still more remote action, in that as the result of the radiation of the body in general certain protein substances are formed that actually stimulate the ovary. Finally, it is possible that the effect is produced, not by stimulation, but by the inhibition or actual destruction of certain structures in the ovary, such as follicular cysts or a persistent corpus luteum. It is the last theory which appeals to me the most.

It would be of great help if Dr. Kaplan could tell us what type of amenorrhea he has been treating. Now it is fairly well recognized that amenorrhea may be of at least two types. In one there is an atrophic ovary and an absence of estrin in the blood and in the urine. In the other type there are probably follicular cysts or persistent corpora lutea in the ovary and here there is still an ovarian function in an endocrine sense which demonstrates itself in the moderate hyperemia of the vaginal mucosa.

It is first of some scientific importance for us to know which type of amenorrhea Dr. Kaplan has been radiating. If these cases are of the atrophic type, then the effect must be some variety of stimulation, whereas if they fall in the group that are connected with follicular cysts or the persistent corpus luteum, the x-ray may have a destructive effect on some of these structures and still regulate the ovarian function.

This differentiation is also of practical importance. We should in fact know before radiating a case of amenorrhea which type we are dealing with. If we have the type of amenorrhea due to a depression of the ovarian function, the x-ray may make it worse. If we have an amenorrhea due to follicular cysts or a persistent corpus luteum, the x-ray may be beneficial.

A number of other writers have published their results following radiation of the ovary for amenorrhea and sterility. These have been collected and reported by Wintz (Wintz, H., and Wittenbeck, F. "Klinik der Gynäkologischen Röntgentherapie." *Handbuch der Gynäkologie*: 6: Part 1, Munich, 1933, J. F. Bergmann, p. 318.) as a series of 319 cases from about twenty different authors. In about 50 per cent of the cases of these authors, improvement in menstruation resulted, and in about 15 per cent pregnancy ensued. As I figure Dr. Kaplan's results, he has obtained about 60 per cent improvement in menstruation and about 33 per cent of the patients became pregnant.

Any results on the treatment of sterility and on abnormalities of menstruation are notoriously difficult to evaluate. I would like to know in detail how long these patients were amenorrheic, how long they were sterile, how soon after treatment they developed menstruation, and how soon after treatment they had children. I think it is very probable that some of Dr. Kaplan's patients would have become pregnant and some of them would have had a normal return of menstruation even without treatment. On the other hand, Dr. Kaplan's results are so good that we cannot deny the probability that the x-ray was an important factor in producing the reported results in many of the cases.

DR. ISIDOR C. RUBIN.—There are two or three points that I want to touch upon. First, there is the danger of an embryo being irradiated without the physician who sends the patient to the x-ray therapist being aware that the patient is pregnant. The treatment should therefore under no circumstances be instituted except within a week after a period no matter what the menstrual habit for that particular

radiated and an abnormal fetus was born. I do not think that was due to the x-ray, although it may have been. X-ray therapy therefore does not always mean an abnormal fetus. I think the error made by the Committee which Dr. Miller referred to, was their failure to state that normal babies were born as well as abnormal ones, and that abnormal ones were born before the x-rays were ever dreamed of.

I cannot answer Dr. Geist's question about the special hormone that is lacking in these cases. All the hormone tests should be preformed, but these are carried out by the gynecologist before we get the patient. We as radiologists are simply asked to treat the case.

With regard to the pituitary, Lacassagne has shown definitely that it takes a powerful dose to destroy the glands and very little pituitary hormone is necessary to make the ovaries function. The dose we give cannot harm the pituitary.

Dr. Cary asked me to define the indications for simple ovarian radiation and for radiation of the ovary and pituitary. We select each case in accordance with personal judgment, based on a series of many cases. If we see a patient with hair on her face, with a big abdomen, thick and fat, we think she needs thyroid plus pituitary plus ovarian stimulation. If she is of short stature and, with some increased hair over the body, and a rather stupid appearance we use pituitary stimulation along with the ovarian.

With reference to subsequent disturbances, there are only two or three cases in which menstruation has again become irregular. All the others had a continuation of normal menstruation. Nine patients had more than one baby; several of them, as you saw in the slides, had three children; and even the patient with twins had two subsequent normal pregnancies.

PATHOLOGY OF THE CERVIX*

WALTER SCHILLER, M.D., VIENNA, AUSTRIA

(*Clinical Pathologist, Weibel Clinic*)

SOME years ago I attempted to get a general view of the results of therapy in carcinoma of the cervix cases by collecting a number of series of statistics. Since 1921 no great improvement has taken place. There is a certain slight difference in statistics of different clinics and laboratories, it is true, but the total results are almost the same. Among 100 women who come to the dispensary and clinic only 50 per cent are operable. Of this 50 per cent, we save by radiation or operation 25 per cent. Twenty-five per cent are lost.

A variation in these figures is introduced by the selection of cases regarded as operable. Brilliant operators have a higher mortality figure and a lower percentage of saved cases, while some men of lesser skill have an astoundingly high percentage of saved cases. The skillful operator's results are poor for the reason that he extends the limits of operation. The above figures mean that we generally can save only one out of four women. What can be done to improve these relatively poor statistics?

We have two methods of treatment, surgery and irradiation. The vaginal operation by Schauta and the abdominal by Wertheim give prob-

*Read, by invitation, before the Chicago Gynecological Society, October 23, 1935.

the corpus luteum. Anybody who uses x-ray much knows that corpus luteum cysts do disappear. We have a follow-up on about twelve hundred patients treated with sterilizing doses of x-ray or radium, the average follow-up interval being seven and a half years, that is from two years up to twenty odd years, and in not a single instance has there developed a so-called cystic ovary. There have been neoplasms of the ovary and cystadenomas, but not one follicular cyst.

DR. WILLIAM H. CARY.—I would like to ask Dr. Kaplan what are the indications for radiation to the ovary only and what for extension of the radiation to the pituitary. Furthermore, I would like to inquire if there has been any follow-up study of the radiated cases and if any subsequent disturbance of the ovary followed.

I note that in many of the patients concerning whom he gave a detailed history there was some degree of obesity. It would clarify results if we could learn whether additional exercise, diet, thyroid extract or other forms of medication were utilized during or subsequent to the x-ray treatment.

DR. FRANCIS W. SOVAK.—I have been particularly interested in one of Dr. Kaplan's cases, a young Italian woman with amenorrhea of many years' standing. She was rather obese with a low basal metabolism and was treated with thyroid extract, exercise, diet and all the kinds of endocrine therapy we knew about at that time. She was referred to Dr. Kaplan by me eight years ago, and has since been delivered of three healthy babies and her menstruation is normal, of the twenty-eight-day type.

DR. IRA I. KAPLAN.—These cases were sent to me by gynecologists or obstetricians, none by the general practitioner. I have assumed that these men carried out all the tests and examinations which they regarded as necessary to establish the indications and diagnosis. I do not establish the gynecologic reasoning for treating the patient, but use my judgment as to the method of treatment.

Dr. Healy asked if these patients were treated by other methods. Insufflation had been done in about 80 per cent of the cases. In the full text of my paper every case is reported in detail and it will be found that practically every case had the various tests which were known at that time, and the later cases had the newer methods of testing patients for functional disturbances.

We had 76 patients that improved out of 128, while 52 did not improve. Actually 14 were lost, so that we have records of only 38 cases that were failures. Seventy-six resumed menstruation, and of those there were 44 that became pregnant.

I cannot report what type of amenorrhea we were dealing with in all of these cases, whether associated with the atrophic ovary or the ovary with follicular cysts. In only one patient who was operated upon, a definitely cystic ovary was found. The adnexa were clinically always reported as being normal.

How soon after treatment do these effects occur and do we treat these cases again? Out of the entire group I think there were only two patients who had subsequent treatment. If we feel that we have failed, we do not risk further treatment after we have given three treatments over a period of three weeks. Very occasionally do we give a fourth treatment. One of the cases in which we gave a fourth treatment is one of the patients now pregnant. We believe it requires four weeks for effective menstruation to restore itself. If it does not restore itself in that time we believe treatment has failed, yet in some cases menstruation was restored even after eight weeks.

With an embryo in the uterus we do not believe radiation should be given. We do not treat even carcinoma in the presence of pregnancy, although we have had one such patient, who was later delivered of a living child. Neill has reported the same thing. Another case, before the days of the Aschheim-Zondek test, was

the invading ulcerating carcinoma as in this surface strip. We must decide whether the chief criterion of cancer is the cytologic characteristics or the quality of invasiveness. I prefer to decide this question from a cytologic point of view and to call this a surface carcinoma or a superficial carcinoma. Kermauner for the first time in gynecology had recognized a carcinoma that showed no point of invasion but was on the surface only.

The first step toward an earlier clinical diagnosis was to get a clearer idea of the histologic character of early carcinoma. The problem was how to obtain a number of carcinomas too small to be discovered by the naked eye. We could not expect such a carcinoma from the dispensary or from the examining gynecologist. I had at first to rely on pure chance and looked for success by examining a great number of cases. Three thousand so-called normal cervixes were examined and it was thus possible not only to find a number of early carcinomas, but also to reconstruct the development of early carcinoma. I was able to divide the cases into three groups. In the first group there were three zones, first of ulceration, second of invasion, and third, what I may call carcinoma manifesting only cytologic characters. In the second group there was no ulceration and a much smaller zone of invasion, adjacent to a strip of carcinomatous epithelium. In the last group there was carcinomatous surface epithelium only, with no invasion and no ulceration, but only changes in the cytologic characteristics. This was the earliest phase of carcinoma we succeeded in recognizing, and it is doubtful if even in the future we are able to find a smaller, younger and earlier phase.

According to the old pathologists we would not be allowed to call this lesion carcinoma, for the old pathologists believed that carcinoma had to be proved by invasion. Some men use the word precancer, but this term is not well defined. Many men are using the term precancer in the sense of potential carcinoma. Others use it to imply the certainty of carcinoma in the future. It is much better to call this finding carcinoma, and characterize it as early carcinoma or still better pre-invasive carcinoma. In biopsy specimens it is not possible to rule out the possibility of invasion in the vicinity of the specimen.

To summarize to this point, two statements are to be noted. First, the early stage of carcinoma is characterized by surface epithelium that has the cytologic characteristics of carcinoma. Second, early carcinoma is identical in structure, cytology, and type of cells with the surface growth at the margins of some advanced carcinomas.

The next question was, how to make surface carcinoma visible to the gynecologists. I found that carcinoma of the cervix can be differentiated from normal epithelium in about a fifth of the cases by three characteristics. First, this zone is a little elevated. Second, the surface is not perfectly smooth and is somewhat dull. Third, while the normal

ably the best results an operative technique can achieve. Irradiation results depend on the type and strength of the rays. Physics and not medicine must discover new rays and new methods of irradiation. Nevertheless, I do not think we can get much farther than about 30 to 32 per cent of cures by irradiation. Thus neither irradiation nor surgery may give us much improvement in the statistics of end-results.

One method of approach is left and that is early diagnosis. All statistics show that the earlier a patient is operated upon or irradiated, the greater is the probability of a permanent cure. In this belief, I decided some time ago to devote my efforts to establishing better ways of early diagnosis.

The early carcinoma and the small one are not identical. If carcinoma grew very rapidly from its onset, then a small cancer would be a young one, but that is not true. Since 1928 I have collected many very early carcinomas, and I have had the opportunity to keep a few of these cases under observation for many years. I was able to prove that in the early stage carcinoma grows very slowly. The curve of development first rises slowly, and then suddenly ascends very rapidly. This fact that carcinoma grows so very slowly at the beginning offers a marvelous chance for early diagnosis. If carcinoma's early phase lasted but a few days, it would be very difficult to get hold of early cases, but its initial phase lasts months, even two or three years or perhaps longer.

Since the expression early carcinoma is more or less accepted, we may perhaps continue to use the term. We must not forget, however, that by it we only mean a small carcinoma. In my investigations I admitted a carcinoma to be a small one if it were too small to be detected by the gynecologist with the ordinary means. For the carcinomas large enough for the gynecologist to find with the naked eye, we need not waste our time trying to find new methods.

In a monograph which Kermanner published with Schottländer on carcinoma of the cervix, he discussed the important question of how the normal epithelium and carcinoma meet one another in advanced cases. In 95 per cent of cases it is found that between the normal epithelium and the carcinoma a zone exists, occupied by neither carcinoma nor by normal epithelium. This zone Kermanner proposed to call the neutral zone or the zone of demarcation. In the remaining 5 per cent of the cases there is instead a small intermediate strip between normal epithelium and carcinoma which is characterized by two points. Under the low power it is seen that the height of this epithelium is exactly the same as that of surface epithelium, but with the high power it is clear that the cellular type is exactly the same as the cells found in carcinoma. How should we classify this strip? Should we say it is normal epithelium or should we say it is carcinoma?

Ordinarily we diagnose carcinoma only if we can demonstrate invasion. The cytologic characteristics are, however, exactly the same in

Although syphilitic leucoplakias are not rare in the mucous membrane of the mouth, they are uncommon in the cervix. In fifteen years of intensive examination of many thousands of slides of the cervix, I succeeded in discovering only three cases of syphilitic leucoplakia. Of these three, we were not perfectly sure of two. This is sufficient to prove that syphilitic leucoplakia is of no great importance.

Epithelium also loses glycogen if it develops keratinization, and this we see not very rarely. If the cervix is exposed to the air it produces horny layers, which appear as white areas of entirely different type. They are not demarcated, are distributed over the cervix, and are of a whitish or yellowish color. The carcinomatous leucoplakia does not change in appearance in a few months or even in a year's time. If you paint a cervix with keratinization two or three times at weekly intervals, you find a changing pattern—like clouds passing over the mahogany brown sky of the cervix. These confluent clouds when present are so characteristic that we rarely have to make a histologic examination.

A fourth exception is found in the fact that only the surface layer contains glycogen. If the surface layer is torn off by trauma, by the examining finger or by the speculum, we see a white area of traumatic origin. It takes a few days to store glycogen again by healing and restitution of normal conditions.

Finally there is another condition of great interest, a sharply demarcated dull white opaque area, which we may see in young individuals of twenty. A biopsy shows it to be a typical hyperkeratosis. I have carefully removed the surface epithelium in some of these cases and a week later the leucoplakia was present again. We can classify these lesions only as we do nevi or other local changes of the skin, as probably congenital abnormalities of the epithelium of the cervix. I propose for this lesion the name leucoplakia leucokeratosis, which we can prove has nothing to do with carcinoma, prolapse, or syphilis of the cervix.

It has never been proved that these cases have a tendency to change into carcinoma, and to convince myself, I have kept a certain number under observation for some years. One of these I watched for five years, another for six years, and in none was I able to find the slightest evidence of transformation into carcinoma. These cases may have a tendency to change into carcinoma, but it is not proved. We are not therefore justified in using radium, but are obliged to keep these cases under observation.

For the differential diagnosis of these types, we rely on histologic examination. For that we need not make a complete excision, for we are not interested in depth, and wish to examine only the surface epithelium. We make this removal of the surface epithelium easily with a sharp curette, elevate the edge of the epithelium and peel it off.

epithelium of the cervix is more or less translucent, so that the entire connective tissue with arteries, veins, and capillaries shines through and has a slightly violet or reddish tinge, the carcinomatous epithelium is opaque and whitish in color. If you describe this early carcinoma you describe it as a white patch or as a leucoplakia. About 30 per cent of all cases of beginning carcinoma gave the appearance of leucoplakia.

Leucoplakia means "white patch." It is not a pathologic entity, but simply a description, a sign, and means no more than if you say fever or jaundice or edema. These are symptoms but not pathologic entities. Similarly, we should not use leucoplakia in the sense of a clinical diagnosis. The relation between leucoplakia and carcinoma is simply that some of the young carcinomas look like leucoplakias.

What is to be done for the remaining 70 per cent of very early carcinomas that are not visible? Attempts to differentiate these carcinomas with a vital stain were unsuccessful, because it was not possible to find a dye that would stain carcinoma and not stain normal epithelium or vice versa. Now the surface layers of normal epithelium are composed of cells which appear empty when hematoxylin eosin stained, but with a special stain can be shown to be filled with glycogen. This glycogen is not analogous to the glycogen of the liver or of muscle, which is soluble in water. The glycogen of the cervix epithelium is not soluble in water, and consequently we can put the slides in water without losing part of the staining glycogen. These glycogen-filled cells are not found in carcinoma, which gives the basis for a differential test.

The method of staining glycogen is to bring it in contact with iodine. Glycogen attracts and stores iodine, and stains a deep brown. We cannot use an alcoholic solution because in that way we produce a surface necrosis, and must depend on an aqueous solution. The best solution is the so-called 1-2-3 solution, which means pure iodine 1 gm., potassium iodide 2 gm., and water 300 cm. We can transform a latent carcinoma into a visible carcinoma by using this solution, the surrounding epithelium staining brown and the carcinoma remaining perfectly white.

The iodine test serves only to discover a carcinomatous zone in a layer of normal epithelium. This test is of no value, for example, in distinguishing between ulcerating carcinoma and erosion. The differential diagnosis between these conditions has to be made by means of a biopsy.

This test, furthermore, serves only to indicate suspicious spots, but does not prove that the white spots are carcinoma. They may be carcinoma, but they may be something else. The brown stain, on the other hand, is perfectly specific, for if the surface epithelium absorbs glycogen and stains brown, it is normal. In carcinomas we see a sharply demarcated field with its central margin in nearly all cases coinciding with the junction of columnar and squamous epithelium at the external os. We never see in these beginning carcinomas a transitional zone between the white and the brown areas.

never been lacerated and that has never been the seat of erosion. These specimens you have seen described tonight prove to you that these cervixes in which we find the earliest stages of carcinoma are not diseased cervixes, but are otherwise perfectly normal cervixes.

I was glad that Dr. Schiller's report showed that one patient died of carcinoma because that is proof that it was a real carcinoma. Without this death, the objection might be sustained that those cases stayed well because they did not have carcinoma.

It is interesting to compare with these results those of Hinselmann. Hinselmann had the good fortune of working in a country where the people are under great governmental control, and as a consequence serve as excellent clinical material. Every woman following labor who is entitled to sick benefits must be examined every year or oftener with the colposcope. Hinselmann collected an enormous material, and he reports also about 130 cases saved by early discovery with the colposcope. Here our propaganda about early diagnosis of carcinoma is a sad failure, and unless we can persuade the patient to come for the regular examinations which Dr. Schiller described, we shall continue to have to deal with hopeless carcinoma.

DR. HENRY SCHMITZ.—May I add a similar observation. In this instance cytologic changes were found in the amputated cervix, similar to those described by the speaker. Six months after this operation the patient returned with a bloody discharge, and on examination friable tissue was found in the left part of the cervix. Microscopic examination of this tissue showed an invasive carcinoma. At this time the case belonged to clinical Group II, that is, a doubtfully localized carcinoma. This happened about four years ago and the patient is well today.

At the time we sent the slides from the first operation to several outstanding pathologists. Half agreed with us that the cytologic changes in the amputated cervix were carcinoma, while the other half denied the existence of carcinoma on account of absence of invasiveness. The course of clinical events evidently proved that the former group was correct. It behooves us to determine now, when atypia of the cells may be diagnosed carcinoma, or at least, a transition stage from a benign inflammatory reaction to a typical carcinoma. If the observations cited by Professor Schiller and by me could be multiplied, the uncertainty could be settled. At any rate the patient should be given the benefit of the doubt and be treated for carcinoma. This may be done with radium without danger of mortality. The control of cervical carcinoma depends on the general practitioner, on his insistence to examine the patients periodically in order to exclude any possibility of abnormal tissue changes anywhere. This would mean very careful examination of the genital organs by palpation and inspection. Women should be taught to insist upon having periodic examinations when consulting a doctor.

In our statistics we have 75 cases in clinical Group I, seen up to 1931. There were 15 patients who had absolutely early and symptomless cases. These 15 patients who were treated adequately were all well at the end of five years, while in the other 60 cases which could be diagnosed clinically, the five-year mortality was about 20 per cent. This shows the importance of treating the patients when they are in the so-called pre-invasive and silent stage.

DR. FREDERICK H. FALLS.—The slow growth of carcinoma of the cervix that Dr. Schiller emphasized is very important. We have under observation now 25 patients in whom we have a negative biopsy, but a positive Schiller test. We are keeping them under close observation to determine the earliest malignant changes if and when they occur.

Will Dr. Schiller discuss the carcinoma that develops from the glands deep in the cervix beyond the columno-squamous junction? It is our impression that there

The incidence of carcinoma is sometimes very high and sometimes very low. The man who examines systematically all cases has a low incidence. The statistics of our dispensary show that in 100 cases there are perhaps 25 with more or less well-developed white spots. Of these 25, one can rule out 10 or 15 as being of the hyperkeratotic or traumatic type. Ten or 15 biopsies must be made and out of these one, two, and sometimes three are carcinomas. I feel satisfied if in 100 cases I find one carcinoma.

It is a mistake to carry out the test in suspicious cases only. We see carcinomas in women who never had leucorrhea, never had a discharge, in women with perfectly smooth cervixes and portios. In the course of the last three or four years I have discovered a number of early carcinomas in young women who came for backache, cystitis, or some other unrelated complaint. If we could examine all women once or twice a year, by the iodine test, then we would succeed in getting all carcinomas in the initial phase and all would have a definite possibility of cure. This point seems to me of great importance.

Since 1928 I have discovered 130 cases of early carcinoma of this type. From 1928 to 1931 there were 51 cases. Of these 51, after five years 49 are alive and perfectly healthy. Two patients have died, of which one was the first case we did. This case may not have been a very early carcinoma because, in later reviewing the specimen, I found a few larger projections. The second patient we lost is a real failure from a clinical point of view, and is pathologically of special importance. This was a perfectly superficial case with almost no downgrowth. We operated upon her and two and one-half years later she developed an extensive recurrence. This one failure proves that these cases were really carcinoma. We have, however, saved 96 per cent, and we have lost only 4 per cent. The iodine test is neither painful nor difficult nor expensive. If it could be carried out systematically on all women, we could extend the probability of a 96 per cent healing to all carcinomas of the cervix.

DISCUSSION

DR. EMIL RIES.—We have been accustomed to the teaching which gives as symptoms of carcinoma, ulceration, foul discharge, cachexia, and anemia. These were considered the proper symptoms to be thought of in the diagnosis of carcinoma. Now we know these symptoms are those of the far advanced, mostly ulcerated carcinomas. We have come now to the point where we can find really early carcinoma, carcinomas that do not show ulceration. We now find carcinoma in women who never suspected it and who have no clinical signs to make them suspected of having carcinoma.

We hear much about erosion and laceration of the cervix as the causes of carcinoma. When investigators found multiplication of the epithelium they were inclined to say, here is beginning carcinoma. Others have been insisting, and I think correctly, that carcinoma is carcinoma from the beginning and that carcinoma occurs as carcinoma and nothing else. It does not arise from erosion, nor does it arise from the lacerated cervix. It occurs as carcinoma on the intact cervix that has

working ten hours a day merely to make colposcopic examinations of all patients. I cannot advise the country doctor or the general practitioner to use the colposcope because it is too complicated and too expensive.

Not even Hinselmann dares to make a diagnosis by the colposcope alone. When he finds suspicious areas these suspicious areas are taken out by biopsy and examined under the microscope. But by staining with iodine, we can find, likewise, these suspicious areas. I believe the colposcope is very valuable for the progressive men of the profession, the specialists. I like to use the colposcope for one purpose. On one side we have the naked eye observation of the organ or the specimen, and on the other hand we have the microscopic slide. There is nothing between to make the connection between the naked eye and the microscopic picture. The use of the colposcope will combine the two. For this purpose I think the colposcope is very valuable.

Carcinoma developing from the cervical glands cannot be discovered by the iodine test. This test helps us only to discover carcinoma of the squamous cell type. Glandular carcinoma in our material of carcinomas of the uterus amounted to 2 per cent only. But I have seen carcinomatous stratified epithelium lining the cervical canal. I do not want to call this a downgrowth, because it is not invasive, it is growing along the surface. I have seen such carcinomas of the cervix extend high up, so you can realize the futility of operating on these carcinomas by low amputation of the cervix. It may happen that a small part of the surface epithelium is left. When we make an amputation of the cervix in a beginning cervical carcinoma we have to make several blocks of tissue and we have to watch most carefully to see whether the cut is within the normal epithelium or not. If we prove carcinomatous epithelium at the cut in one slide only, then we know there is the same carcinoma higher up, which will make a recurrence that has to be extirpated by a second operation or, much better, treated by radium.

Concerning the point of origin of carcinoma, I would say that cervix carcinoma begins in the area of squamous epithelium at the point where the columnar epithelium and the squamous epithelium meet each other.

Concerning the question of the further development of these initial carcinomas, we should have few opportunities to make such observations, for carcinoma once diagnosed has to be destroyed. But sometimes we fail. Such clinical failures can occur for two reasons, either the carcinoma was not diagnosed or the diagnosis was made and the patient did not come in to be operated or irradiated. I have made observations of both types. In 1922, at a time when we were not familiar with these initial findings, I made a diagnosis of suspicious epithelium. The patient was dismissed and ordered to come back in a few weeks, but did not come. Six years later, on revising my slides, I came across the old slide and now diagnosed surface carcinoma. I succeeded in getting the patient back to the hospital. I was very much astonished to see that the carcinoma had not made an extension of more than 6 or 8 millimeters. In 1929 I made a scraping from a patient, diagnosed carcinoma, and advised operation and irradiation. She refused on the ground that she felt perfectly well. A few years later I succeeded in getting her back and found that the carcinoma had increased only 2 or 3 mm. in length, with two little projections on one side and one larger projection on the other.

are a considerable number of carcinomas of the cervix that occur in this location. In cases of chronic cervicitis which show areas suspicious for carcinoma by the Schiller test we do a Sturmdorf operation. We split the excised cone from the internal os to the external os and stain with Lugol's solution; all suspicious areas are blocked. Usually we make eight blocks from each cone. If metaplasia is found, we make numerous sections of that block at different levels. The reason we do this is because we have seen single biopsy specimens from which six slides were taken at different levels; four were absolutely negative and two positive showing carcinoma in the invasive stage.

We have a gynecologic resident in the four large state institutions for the insane in this area. We are doing routine Schiller tests on these patients twice a year in an attempt to eliminate carcinoma from this group.

DR. CAREY CULBERTSON.—I have frequently been asked if it is necessary in every case of erosion to have a biopsy. My reply is that it is necessary to have a biopsy if you are looking for something more than you think the patient has. If you think the patient has an erosion you have a right to look for carcinoma. Without a biopsy you cannot recognize it. Dr. Schiller has emphasized the ease with which this material can be obtained. It is not necessary in every case to take off a little wedge in order to make a microscopic examination. This material will peel off like an onion skin with a sharp curette or a sharp edged scalpel.

There have been in recent years some claims by certain clinicians or pathologists that in leucoplakia we have a definite malignancy, that is, that the leucoplakia is cancerous from the beginning. Dr. Schiller has shown us very clearly why in some cases that is so and why in others that is not so.

DR. FRED L. ADAIR.—There are several possibilities that must be considered in connection with the diagnosis and cure of these cases diagnosed as early or superficial or pre-invasive carcinoma. These things have been considered in connection with other types of carcinoma, and must be considered in relation to the ultimate results of treatment of these very early cases. There is possibility, as has already been mentioned, that some of these cases may have been misdiagnosed. We must not forget that though Dr. Schiller is an expert in diagnosis, he may err in diagnosis of early carcinoma. It must be remembered that others less expert than he may make relatively frequent errors in diagnosis and that a certain number of cases which are benign will be diagnosed as carcinoma and others which are malignant will be thought to be benign. It behooves us, therefore, to be careful in accepting these microscopic diagnoses of these early lesions as infallible. Another possibility is this: It has long been known that certain cases of carcinoma may undergo spontaneous cure. If these cases are diagnosed early, there still remains the possibility that some of these very early superficial types of carcinoma may undergo spontaneous cure.

DR. H. M. MARYAN.—Dr. Schiller states that carcinoma occurs at the mucocutaneous junction, likewise Hinselmann. Yet we cannot overlook the fact that we do have glandular changes. What is the relation between the glandular changes and the superficial changes?

DR. SCHILLER (closing).—There is now no competition between the iodine painting on the one hand and the use of the colposcope on the other. Hinselmann uses both. We have only to compare the results of the iodine painting alone with iodine painting plus the colposcope. We do see most interesting details with the colposcope. But on the other hand the colposcope is expensive and heavy, and it takes a long time to learn its use. If you consider that in a dispensary like ours in Vienna we see 80 to 90 new patients in one morning, we would need five or six men

extreme shifts in the hydrogen ion concentration were necessary even to be fungistatic. Thus the principal value of the alkaline douche now seems to be that of a mechanical cleansing agent. The explanation for the prompt relief of symptoms, in the first twenty-four to forty-eight hours postpartum, now appears to be more likely a result in physiologic alteration rather than a change in hydrogen ion concentration in the vagina caused by the lochia. The incidence of fungi in the vagina of pregnant patients increases as pregnancy advances. Woodruff and Hesseltine¹⁴ found 14 per cent in white lying-in patients, 33 per cent in white, and 41 per cent in colored stockyard patients.

PROCEDURE

Inasmuch as a more detailed description of this proceeding has been published by Hesseltine and Hopkins,² it may be stated briefly as follows:

Strain 49 (*Monilia albicans*) was arbitrarily chosen as the test organism. Actively growing 24 to 48 cultures on Sabouraud's media were transplanted into glucose broth. After eighteen to thirty hours, usually twenty-four hours, the tests were made by taking equal parts of well-suspended culture and the chemical. These were thoroughly agitated and at the five-minute interval one loopful (size 3) was transferred to a Petri dish into which Sabouraud agar was subsequently poured and the contents mixed by gentle inclination with rotation. These plates were read in forty-eight to seventy-two hours or sooner if growth appeared. The reading was made in comparison to the controls. (This is similar to F.D.A. procedure.) The chemicals were added in clinically usable concentration. Thus the final dilution was one-half this amount, yet this corresponds in part to dilution in the body. Table I includes all of the chemicals thus far tested. It may be noted that 20 of the 84 materials were sufficiently fungicidal to warrant further evaluation which is given below. Another point of importance is that alcohol and alcohol-acetone-water, both exerted definite but incomplete killing power. Throughout the study, water alone was employed as the solvent unless otherwise indicated except when only slight amounts of alkalies or some such substance were necessary to effect solubility of the compound. This illustrated very distinctly the importance of some vehicles, and this clearly indicated the necessity for adequate control in such researches. Again it was surprising to observe the ineffectiveness of some substances which have received particular recommendation for clinical use. In a few instances the test materials were examined with serum and cells present but were included in this table to show the total number of chemicals examined.

Because the cellular materials and body fluid on the vulva and in the vagina would likely decrease any drug action, human serum and red blood cells were added for tests with the more promising compounds. It is theoretically possible that some of those compounds which were not effective in vitro might behave differently in vivo but as yet there is no positive data or even suggestive evidence of it. Here one part of serum and cells (100,000 to 400,000 per c.mm.) were mixed with one-fifth part of well-laden inoculum after which one part of chemical was added (Table II). These ingredients were thoroughly mixed by shaking and after five minutes a No. 3 loopful was transferred to the Petri dish as above. The readings were made at the same time intervals. One may see at once that the fungicidal power has in

EXPERIMENTAL AND CLINICAL THERAPY OF VULVOVAGINAL MYCOSES*

H. CLOSE HESSELTINE, M.S., M.D., CHICAGO, ILL.

*(From the Department of Obstetrics and Gynecology, The University of Chicago
and the Chicago Lying-In Hospital)*

EVEN though certain therapeutic agents and measures may be satisfactory under given conditions, any investigation which may improve the efficacy, facility, convenience, safety, or economy of these agents or their method of administration is not only interesting but practical.

This particular study on the yeastlike fungi (monilia and cryptococci) was activated because it was often difficult or impossible for the vulvovaginal mycotic patients to return 3 to 6 times a week to receive 1 per cent aqueous gentian violet topical application, and because less frequent visits even with various kinds of daily douches at home failed many times to cure or even improve the condition. However, the results at the Chicago Lying-In Hospital and dispensary confirm the reports of Plass and his coworkers¹ when daily or bidaily treatments can be given. Many substances found unsatisfactory by other workers were not used in this study, and in general only those of the more promising nature along with a few newer and unevaluated compounds were observed in vitro. Those found promising were then tested in the presence of serum and red blood cells and against several strains of monilia. Only a few out of 84 substances were sufficiently promising by these methods to try clinically. Element iodine behavior warranted its trial. Certain problems of administration arose and now appear, partially if not completely, settled.

LITERATURE

Hesseltine and Hopkins² have reviewed the publications of Kolmer and Schamberg;³ Kingery and Adkisson;⁴ Kadisch;⁵ Klarmann, Shternov, and Gates;^{6, 7} Yi;⁸ Emmons;⁹ McCrea;¹⁰ and Woodward, Kingery, and Williams.¹¹ There are perhaps a few other reports which might apply to the obstetric and gynecologic problem, but most of the other data is very limited and generally from uncontrolled series.

Emmons⁹ and Woodward, Kingery, and Williams¹¹ in determining the comparative fungicidal potency of a number of chemicals demonstrated that element iodine was the best. However, these workers did not investigate many of the substances given below and furthermore confirmations were appropos. The reports of Plass, Hesseltine and Borts,¹ and of Hesseltine¹² later, contained advice that sodium bicarbonate douches were helpful, but recently Hesseltine and Noonan¹³ found that

*Read before the Chicago Gynecological Society, January 15, 1937.

TABLE II. FUNGICIDAL ACTION OF COMPOUNDS TESTED AGAINST MONILIA ALBICANS (STRAIN 94)

Exposure Time 5 Min. 0 = No Growth + + + + Growth = Control

	CONCEN- TRATION PER CENT	GROWTH		CONCEN- TRATION PER CENT	GROWTH
<i>Acids</i>					
Benzoic acid	†0.5	0	Pyrogallie acid	0.15	+++
Boric acid	2.0	+++	Pyroligneous acid	2.5	+++
Cinnamic acid	†1.25	++++	Salicylic acid	†0.5	0
Lactic acid	5.0	++++	Sulphosalicylic acid	0.25	++
Perechloric acid	0.05	++	Trichloroacetic acid	0.05	++++
Pieric acid	0.5	++++			
<i>Dyes</i>					
Acriflavine	0.5	+++	Mereurochrome	5.0	++++
Brilliant green	0.5	+++	Mereurophen	0.05	0
Crystal violet	0.5	0	Metaphen	†0.25	0
Gentian violet	0.5	++++	Methylene blue	0.5	+++
Mallophone	2.0	++	Pyridium	0.5	++
<i>Halogens and Halogen Compounds</i>					
Chiniofon	1.66"	+++	Mercuric chloride	0.05	0
Chloramine	0.5	0	Mercuric iodide	0.05	0
Chlorisothymol	†0.1	0	Potassium chlorate	0.25	++++
Chlorothymol	†0.1	0	Potassium iodate	5.0	++++
Dettol	2.08*	++	Sodium chloro-ortho-phenylphenate (dowicide C)	0.05	0
Diiodoquin	10.4	++++	Sodium fluoride	0.5	+++
Iodex powder	5.0	+++	Sodium hypobromite	0.14	+++
Iodine, tincture iodine	0.5	0	Sodium chlorite	0.1	0
Lugol's solution	0.5	0	Sodium iodite	0.5	+++
Glycerin solution (Colloid) "safety iodine"	2.0	0	Sodium tetrachlorphenate (dowicide F)	0.05	+
Iodoacetic acid	0.5	++++			
Iodoajic acid	1.0	+++			

*,†See footnotes to Table I.

TABLE III. INFLUENCE OF HUMAN SERUM AND RED CELLS ON FUNGICIDAL ACTION OF CERTAIN COMPOUNDS WHEN TESTED AGAINST MONILIA ALBICANS (STRAIN 94)*†

Exposure Time 5 Min. 0 = No Growth + + + + Growth = Control

	CONCEN- TRATION PER CENT	GROWTH		CONCEN- TRATION PER CENT	GROWTH
Benzoic acid	0.2	++	Mercuric iodide	0.01	+
Salicylic acid	0.4	+	Sodium chloro-ortho-phenylphenate	0.1	+
Crystal violet	0.4	+	Sodium hypochlorite	0.1	+
Metaphen (tincture)	0.08	+++	Sodium tetrachlorphenate	0.1	+++
Chloramine	0.4	+++	Gold chloride	0.04	+++
Chlorisothymol	0.2	+	Phenylmercuric nitrate	0.01	0
Chlorothymol	0.4	0	Sodium thiosulphate	4.17	+++
Iodine, tincture iodine	0.7	0	Cresol	0.4	+++
Lugol's solution	0.5	0	Hexylresorcinol	0.04	+++
Glycerin solution (Colloid) "safety iodine"	0.4	+++	Mercuric solution	0.0	+++
Mercuric chloride	0.04	0	Thymol	0.1	+++

*Ratio of chemical solution, serum and cells and inoculum = 1:—1, and 0.2 respectively.

†Part of these data are taken from Hoeseltine and Hopkins.

some instances been very much decreased or completely lost under these circumstances, and in not a single instance was the fungous-killing power enhanced.

TABLE I. FUNGICIDAL ACTION OF COMPOUNDS TESTED AGAINST *MONILIA ALBICANS*†
(STRAIN 94)

	CONCEN- TRATION PER CENT	GROWTH		CONCEN- TRATION PER CENT	GROWTH
<i>Other Metal Compounds</i>					
Acetarsonc (stovarsol)	2.5	++++	Potassium antimony tar- trate	0.5	++++
Aluminum sulphate	2.0	+++	Potassium permanganate	0.05	++++
Argyrol	5.0	++	Silver nitrate	0.5	++++
Aurium ammonium suc- cinimide	0.5	++++	Sodium bicarbonate	20.0	++++
Copper sulphate	2.0	+++	Sodium borate	5.0	+++
Gold chloride	0.1*	++++	Sodium perborate	0.5	++
Lead acetate	0.5	+++	Sodium ricinoleate	1.0	++++
Merthiolate	0.05	+++	Sodium salicylate	2.0	++++
Neocarsphenamine	1.0	++++	Sodium thiosulphate	4.17*	++++
Neosilvol	5.0	++++	Stannous chloride	2.0	+++
Phenylmercuric chloride	0.05	+++	Zinc sulphate	2.0	++++
Phenylmercuric nitrate	0.04*	0			
<i>Other Compounds</i>					
Acetaldehyde	0.75	++++	Phenol	0.5	++++
Cresol	0.5	0	Quinine dihydrochloride	5.0	++++
Formol	0.05	+++	Resorcinol	1.25	++++
Furfuraldehyde	2.0	++++	Thymol	12.5	0
Hexylresorcinol	0.05	0	Urotropin	0.5	++++
Mereresin solution	9.0*	+++			
<i>Vehicles</i>					
Alcohol	47	+	Kaolin (suspension)	10	++++
Alcohol	25	+++	Potassium iodide	5	++++
Alcohol acetone water	25-5-20	++	Water (added to cul- ture)	50	++++ (diluted only)
Glycerin	1½ U.S.P.	++++			

*Tested with serum and cells present.

†Alcohol and/or other solvents used with water. Elsewhere water and broth only solvents.

‡Part of these data are taken from that of Hesseltine and Hopkins.

It is a well-known fact that any given antiseptic may not be equally effective upon even similar strains while the difference may be more pronounced with unrelated organisms and since Chlorothymol, mercuric chloride, mercuric iodide, phenyl-mercuric nitrate and element iodines still held fungicidal promise, seven other strains were selected as test organisms (Table III). These included one *saccharomyces* (F. 40), one *cryptococcus* (119), four *monilia* (104, 120, 155, and 156) and one *endomyces** (56924). The monilial strain 155 was an atypical one with variable fermentation powers. Serum and red blood cells were used here as above. At a glance strain resistance variability is

*Obtained from Dr. W. D. Stovall, University of Wisconsin.

TABLE IV. TEST WITH A NUMBER OF YEASTLIKE ORGANISMS IN BROTH WITH HUMAN SERUM AND RED CELLS ADDED*
Exposure Time Five Minutes. +++ Growth = Control.

	FINAL CONCENTRATION PER CENT	ORGANISMS TESTED						
		P40	104	119	120	155	156	56924
Chloroethynol iodine	0.21	0	+++	++	+	0	++	0
Lugol's solution	1.03	0	0	0	0	0	0	0
"Safety iodine"	1.64	not run	0	0	0	0	0	0
Mercuric chloride	0.04	+	+++	++++	++	0	++	++++
Mercuraphen	0.08	not run	++	0	0	0	0	++
Phenyl mercuric nitrate	0.04	0	0	0	0	0	0	0

*From Hesseffine and Hopkins.

conspicuous. If phenyl mercuric nitrate is precipitated by acids then conceivably its action in the vagina would be decreased. Thus, element iodine alone appeared most worthy of study as a practical therapeutic agent. Objections may be made against element iodine, because it may be irritating and even injurious to tissue in infrequent instances.

It was hoped that an iodine preparation might be found which would have the same fungicidal action as the element iodine, or possibly a compound that would liberate element iodine in a harmless manner and yet remain clinically applicable. Dr. W. J. Dieckmann¹⁶ suggested the use of potassium iodate (KIO_3) and potassium iodide (KI). According to Peters and Van Slyke¹⁵ $2\text{KIO}_3 + 10\text{KI} + 12\text{HCl} = 12\text{KCl} + 6\text{H}_2\text{O} + 6\text{I}_2$ (Table IV). Moreover, for each mole of element iodine one needs a mole of KI to carry the liberated I_2 in solution. This necessitates the addition of three more moles, which gives a ration of 1 potassium iodate (KIO_3) to 8 potassium iodide (KI) or molecular weight ratios of 214 to 1328 (that is $1 = 214$ to $8-166$), respectively. Thus, in practice for every unit weight of potassium iodate add 6.2 units weight of potassium iodide. This mixture will yield theoretically 49.3 per cent I_2 or practically one-half.

When these two halogen compounds are accordingly mixed and applied to the adult vagina, the anticipated chemical reaction is completed by the vaginal acids. Unfortunately the quick reactions were too irritating and thus as such were not practical. Since other sources of element iodine were not immediately clear, or did not seem feasible, an attempt was then made to slow up the reaction and at the same time arrange for daily treatment, most of which the patient could self-administer. Because these fungi are limited to the vagina and vulva and do not appear to invade the cervix, self-administration might be tried justifiably.

Even with the chemical behavior so well established it remained necessary to test these two chemicals individually and together as fungicides. Strain 94 was the test organism and Table V shows that both potassium iodide and potassium iodate lack any appreciable fungicidal power either with or without the addition of N/1 lactic acid. Kaolin was also tested and found to be ineffective. Potassium iodate-potassium iodide mixture (ratio 1-8 moles or 1-6.2 wt.) held no promise without acid, but with acidulation the complete killing power extended down to 1.5 per cent concentration of the mixture or 0.7 per cent I_2 equivalent. Even a 1 per cent mixture, 0.49 per cent I_2 value, had distinct but incomplete action within five minutes.

Table VI also presents additional evidence that the mixture of these two iodine compounds may have a therapeutic value because all fungi were killed in 7 other test strains (1 *saccharomyces* F40, 1 *cryptococcus* 119, and 5 *monilia*). The one mold growth on 155 was a contamination because it was unrelated morphologically to the test stain.

TABLE VIII. RESULTS OF IODINE AND IODINE COMPOUNDS USED IN TREATMENT OF ADULT VULVOVAGINAL MYCOSES (YEASTLIKE)

			TREATMENT		
			TYPE	WEEKS	COMMENTS
1	41750	Preg. 3rd§	*Supp. + Iod.	4	Improved, when de- livered
2	46829	Preg. 3rd	Supp. + Usual	2	Improved, when de- livered
3	59934	Preg. 3rd	Supp. + ½% Lys.	4	Cured
4	128488	Preg. 3rd	Supp. + Lug.	2	Cured
5	149822	Preg. 3rd	Cap. + Lug.	1	Treatment not ac- cepted
6	158876	Preg. 3rd	Cap. + Lug.	3	Cured
7	158895	Preg. 3rd	Cap. + Lug.	1	Cured
8	159334	Preg. 3rd	Cap. + Lug.	1	Improving, thus far
9	159855	Preg. 3rd	Cap. + Lug.	1	Improving, thus far
10	159864	Preg. 3rd	‡Cap. + Lug.	1	Improved, but irri- tated
11	161893	Preg. 1st	Cap. + Lug.	2	Improving, thus far
12	162988	Preg. 3rd	Cap. + Lug.	1	Improving, thus far
13	St. Yd.—A	Preg. 3rd	Cap.	2	Improving, thus far
14	St. Yd.—B	Preg. 3rd	‡Cap.	3	Improving, thus far
15	St. Yd.—C	Preg. 3rd	‡Cap.	1	Improving, thus far
16	St. Yd.—D	Preg. 3rd	Cap.	1	Improving, thus far
17	St. Yd.—E	Preg. 3rd	‡Cap.	1	Improving, thus far
18	113321—1	Nonpreg.	Supp. + Iod.	2	Cured
19	113321—2†	Nonpreg.	Supp. + Iod.	2	Cured
20	136860	Nonpreg.	Supp. + I ₂ + KAO.	4	Cured
21	145097—1	Nonpreg.	Supp. + Iod. Changed to Cap. + Lug.	3 2	Apparently cured
22	145097—2†	Nonpreg.	‡Cap. + Iod.	6	Cure now near
23	153228	Nonpreg.	Cap. + Iod.	2	Cured
24	161743	Nonpreg.	Cap. + Lug.	2	Cured
25	D. E.—1	Nonpreg.	Cap. + Lug.	3	Apparently cured
26	D. E.—2†	Nonpreg.	Cap. + Lug.	3	Cured

*Supp., 0.2 gm. KIO₃+KI in gelatin-glycerin suppositories.

Cap., 0.25 or 0.125 gm. KIO₃+KI in kaolin in capsule.

Iod., Iodex powder.

½% Lys., ½% lysol douche daily.

Lug., Application of diluted Lugol's solution at weekly clinic visits.

I+KAO., 10 to 20% element iodine in kaolin.

†Reinfection or recurrence.

‡Did not improve satisfactorily under usual treatment (gentian violet, etc.).

§Preg., Pregnancy and trimester. Nonpreg., nonpregnant.

mixture have at times given only slight indication of iodine liberation. Table VIII shows the results of those treated or still under treatment. The general procedure now in effect after establishing the diagnosis is first to gently wipe the vagina clean and then paint the entire vaginal and vulval walls with a diluted Lugol's solution. If the patient can tolerate one-fourth strength, it is used and a stronger solution used the following week, while if it irritates, greater dilution is recommended. The patient is given capsules (size 00) each containing the iodine mixture (1½ gm.) in kaolin with the direction to insert one into the vagina each evening and return in one week. Other deviations have been 1½ gm. per 00 capsule and ¼ gm. in number 12 veterinarian. In the table a few notations indicate that Iodex powder* was

*Munby and James, Ltd., voluntarily donated the Iodex materials.

TABLE V

1 KIO ₃ + 5 KI + 6 HCl = 6 KCl + 3 H ₂ O + 3 I ₂ .
Thus 5 moles of KI are necessary to produce the iodine and 3 additional ones are required to carry it in solution.
This gives by molar weight a ratio of 1 to 8 of KIO ₃ to KI.
Since 1 molar weight KIO ₃ = 214 approx. and 8 KI = (8 × 166) 1328 approx..
use by weight 1 gm. KIO ₃ to 6.2 grams KI.
1 KIO ₃ + 8 KI should yield 3 I ₂ or about 49.3 per cent by weight.

TABLE VI. POTASSIUM IODATE AND POTASSIUM IODIDE AS FUNGICIDES AGAINST STRAIN 94 (MONILIA ALBICANS)

Exposure Time 5 Min.	0 = No Growth.		++++ = Control Growth.	
NONACIDULATED				
	CONCENTRA- TION %	APPROX. I ₂ %		ACIDULATED
Potassium iodate	5	0	++++	++++
Potassium iodide	5	0	++++	++++
Kaolin	10 (Suspend- sion)	0	++++	Not run
KIO ₃ + KI	4	1.8	++++	0
KIO ₃ + KI	2	0.9	++++	0
KIO ₃ + KI	1.5	0.7	++++	0
KIO ₃ + KI	1.0	0.49	++++	++

TABLE VII. POTASSIUM IODATE-POTASSIUM IODIDE MIXTURE AS A FUNGICIDE WHEN ACIDULATED* IN PRESENCE OF SERUM AND RED BLOOD CELLS WITH SEVEN OTHER STRAINS OF FUNGI

CONCENTRATION									
Mixture % (KIO ₃ + 8KI)	1.5	Potential I ₂ 0.7	F40 Approx.	119 0	104 0	120 0	155 1 mold	156 0	170 0
							colony		

*Acidulated with N/1 Lactic Acid
0 = No Growth +++++ = Control

The first attempt to slow up the reaction was by incorporating the iodine mixture in gelatin and glycerin suppositories. However, the acidity of the gelatin allowed the liberation of iodine on standing and thus permitted a too rapid action of the halogen when the suppository was inserted into the vagina. The second choice was kaolin (a native hydrated aluminum silicate). Because it is treated with acid for purification it is necessary to neutralize the material. This has been done by using ammonia vapor and then desiccating the kaolin to remove the excess ammonia. When sufficient dilution of the iodine compounds was made with this powder, the reaction was slowed and has given clinical results sufficiently good to encourage further observation along this general direction.

No doubt other and perhaps better methods may be revealed. It seems reasonable to believe that if the gelatin-glycerin suppositories are neutralized without leaving excess alkali that they might be satisfactory vehicles. The gelatin capsules containing the kaolin iodine

7. The patient should be advised about and against the possible sources of reinfection.

8. A relationship between the in vitro and in vivo experiments has been described.

The author is much indebted to Dr. Adair and all the members of his department for their cooperation. Mr. Cooke of the University Clinic Pharmacy made the capsules for clinical use.

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THE ORAL ADMINISTRATION OF PARALDEHYDE FOR RELIEF OF PAIN DURING LABOR*

EDWIN J. DeCOSTA, M.D., AND RALPH A. REIS, M.D., CHICAGO, ILL.

(From the Department of Obstetrics, Michael Reese Hospital)

IN CONSIDERING the management of labor from the viewpoint of pain relief, it is essential to decide at the outset just what degree of relief is to be sought, particularly with regard to the available facilities for nursing the patient. There is great danger involved in rendering a patient unconscious or even in masking her symptoms by the use of powerful agents, except in institutions in which constant medical and nursing care is available. Narcosis should not be recommended for general use since few institutions are sufficiently well regulated and staffed to warrant such routine medication. It is even debatable whether or not a state of narcosis is desirable from the viewpoint of its psychologic effect on the mother and its effect on the physiologic course of labor.

This presentation is a study of the effects of varying doses of paraldehyde on the course of labor and on the accompanying degree of analgesia and amnesia.

Paraldehyde $(CH_3CHO)_3$ was introduced by Cervello as a powerful hypnotic about fifty years ago. This polymer of acetaldehyde (CH_3CHO) is a volatile, colorless, transparent, inflammable fluid, slightly soluble

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UNIVERSITY OF WASHINGTON
SCHOOL OF NURSING
HARBORVIEW DIVISION.

HESELTIME: EXPERIMENTAL THERAPY OF VULVOVAGINAL MYCOSES 447

tried. In a series not included here it gave disappointing results. The plain iodex ointment gave some patients with vulval mycosis relief but not reliably so. Ordinarily douches should be infrequently used, if at all, while employing this procedure. If a vaginal douche must be taken, lysol or biichloride of mercury are the two most logical medicaments in the absence of free iodine, as one may observe in the foregoing tables.

Because the monilia and cryptococci can be conveyed to the genitals through fungous contamination of hands, clothes, fecal material and phallus, the patient should be instructed about the danger of reinfection. One patient in this series had a mycosis develop in the usual incubation period following a known contamination of the vulva with fecal material. The same fungi were recovered from the rectum. The fungi survive until killed off or the environment becomes unfavorable. The vaginal epithelium of women of the reproductive period and especially in pregnancy is rich in glycogen-like material which is converted into available carbohydrate substances. The constant spill of glucose over the vulva by diabetic patients produces another favorable environment for growth of fungi. The vulva and vagina of the premenstrual patient are almost never attacked and the postmenstrual individual has nearly the same freedom from fungi in the absence of diabetes.

SUMMARY AND CONCLUSIONS

Although this series is small it represents a large number of clinical patients because only those patients with sufficient symptoms to unsolicitedly complain are included. The milder ones and carriers may be treated very successfully by the usual means of gentian violet and respond quickly to the above described procedure. The severe infections and the old chronic ones may present a real therapeutic problem at times.

1. It appears that definite improvement can still be made in mycotic therapy but certainly iodine in the element form or some equally active fungicidal compound will be a part of the answer.

2. Further investigation on vehicles is recommended.

3. One per cent gentian violet is still recommended for oral thrush.

4. The fungicidal action of potassium iodate and potassium iodide, in a ratio of 1 to 6.2 gm. in the presence of an acid, has been demonstrated.

5. The preparation described and the procedure outlined has given better results so far than the dye method when less frequent visits are necessary.

6. Adequate observations are advisable to avoid tissue injury in exceptionally sensitive patients.

for each twenty pounds of body weight; this was emulsified with an equal volume of almond oil and orange juice, and chilled. Vomiting was minimized when the stomach was empty. Somnolence in the mother occurred within ten to fifteen minutes and the hypnotic effect usually lasted four to six hours.

In the second series a similar paraldehyde emulsion was given in smaller dosage. Here, response to the first dose of 15 c.c. was used as an index for subsequent medication. A second 15 c.c. dose was frequently given thirty to sixty minutes later. Usually two doses sufficed, giving relief of four to six hours' duration. Additional 8 c.c. doses were administered every two to three hours as needed, in prolonged labor.

In the third group, paraldehyde was administered in 1 c.c. gelatine capsules. The initial dose was four capsules, and this was repeated every hour until the desired hypnotic effect was secured. The maximum total quantity given was 28 c.c. during a seventeen-hour period.

TABLE I

	FIRST SERIES	SECOND SERIES	THIRD SERIES
Amnesia			
None	3	2	25
Partial	13	6	0
Complete	9	17	0
Analgesia			
Poor	2	2	10
Fair	13	5	15
Excellent	10	18	0
Response			
Excited	6	0	0
Restless	9	7	0
Quiet	10	18	25
Delivery			
Spontaneous	12	7	18
Low forceps	13	15	7
Midforceps	0	2	0
High forceps	0	1	0

The response to paraldehyde was quite different in these three groups. In Series I, where one large, almost knockout dose of 25 to 40 c.c. was given, only 40 per cent were quiet, while 36 per cent were restless and 24 per cent truly excited. Complete pain relief was obtained in 40 per cent, partial in 52 per cent, and little or none in 8 per cent. Amnesia paralleled analgesia, being complete in 36 per cent, partial in 52 per cent, and poor in 12 per cent. Twenty-eight per cent in this group vomited ten minutes to two hours after taking the medication. When vomiting occurred within one-half hour, half the preceding dose was repeated. The average duration of labor was sixteen hours, thirty-four minutes, and the average length of labor after paraldehyde was given was five hours and two minutes. Spontaneous delivery occurred in 48 per cent; low forceps were used in 52 per cent.

The second series was more encouraging. The average individual dose was only 15 c.c. but the total dosage frequently reached 45 c.c. Seventy-two per cent were quiet, 28 per cent restless and none excited. Analgesia was excellent in 72 per cent, fair in 20 per cent, and poor in 8 per cent, while amnesia was complete in 68 per cent, partial in 24 per cent, and absent in 8 per cent. Vomiting occurred more frequently, being present in 48 per cent. The total duration of labor averaged nineteen hours, thirty-seven minutes, while the average time following the last dose of paraldehyde until delivery was four hours, forty-one minutes.

in water (1:8) and freely miscible with alcohol and various oils. Pharmacologically it resembles ethyl alcohol, is rapidly absorbed from mucous membranes and rapidly excreted from the body through the lungs and kidneys without damage to these organs. Its disagreeable, pungent taste and irritating effect on mucous membranes have limited its use in spite of its extremely low toxicity, absence of respiratory and cardiac depression and prompt hypnotic action.

Oral administration is distinctly preferable to rectal because of the ease of administration and the certainty and promptness of systemic action. Rectal administration during labor is not compatible with rectal examination until absorption is complete. Recent reports concern themselves only with rectal administration. This choice of the less desirable route may be based largely on the unpleasant taste of the drug.

The disagreeable taste and odor are inherent in paraldehyde. Numerous attempts have been made to mask these by incorporating paraldehyde in suitably flavored vehicles. Throat irritation can be partially relieved by dissolving the drug in a bland oil. A chilled emulsion with orange juice and oil has proved a fairly satisfactory preparation. The chief objection to disguising paraldehyde is that the total quantity administered is thereby increased and the disguise is still quite transparent. This difficulty can be overcome by giving paraldehyde in a gelatine capsule. Paraldehyde hardens gelatine and renders it insoluble in water; therefore the capsule should be filled just before use. A No. 00 capsule holds exactly 1 c.c. and is easily swallowed. The taste problem is thus satisfactorily solved but the quantity that can be given with ease is limited.

Previous investigators, with the exception of Kane and Roth, have combined paraldehyde with other drugs, particularly barbiturates, in the belief that paraldehyde itself was not analgesic. This belief may be traced to Sollmann. Most authors, when considering restlessness, ascribe it also to the adjuvant barbiturate. The accuracy of these statements will be considered in the present study.

The oral use of paraldehyde during labor was begun at Michael Reese Hospital about a year ago. This study has been empiric from the outset since neither oral dosage nor a pleasant means of administration was known. Paraldehyde was given by three methods to groups of twenty-five patients each. These patients do not represent consecutive admissions. In many, labor was too far advanced at the time of admission to permit satisfactory trial, and frequently the general maternity service was too active to allow careful nursing and observation.

An attempt was made in the preliminary group to ease the last few hours of labor by a single massive dose of paraldehyde. Four cubic centimeters were given

tion and forceful contractions recurred at three-minute intervals. These criteria were of little aid in managing the labor and finally were dropped, paraldehyde being given when the patient was actively in labor and complaining of painful contractions, without regard to the cervix, membranes, or parity.

The threshold of pain appreciation is in itself most variable. Some investigators believe that a normal labor is relatively painless, and that discomfort arises from psychic stimuli, especially fear. These stimuli are supposed to act through the sympathetic nervous system causing constriction of the circular fibers of the uterus, increasing the resistance to dilatation. This prolongs labor and increases pain perception. There is clinical evidence that an element of truth may be present in the foregoing. Fear, anxiety, and worry are known to cause spasticity in other organs containing unstriated muscle. Abnormal conditions in these organs frequently are cured by suggestion and faith. So too during labor, the calm, relaxed patient who has faith in her physician frequently has a rapid, more or less painless delivery; while the tense, fearful patient drags on for hours with no apparent reason for delay. It has long been observed that certain physicians enjoy success with a procedure that fails in the hands of others, that one person administering an analgesic gets better results than another, and that cultists succeed where doctors have failed. How else can we explain these facts unless we accept the influence of the mind over bodily function? Perhaps it is in this respect that paraldehyde in small doses seems so efficacious—it aids the patient to relax and labor follows a more normal course, less influenced by the untoward stimuli that may arise from lay misconceptions of the normal process of delivery.

As shown by Moore and McCurdy, and Kane and Roth, paraldehyde in 30 to 40 c.c. doses did not significantly change the frequency or strength of uterine contractions. In this series, when small individual doses were used, contractions seemed stronger and more frequent.

With all three methods of medication, the pulse, respiration, blood pressure, and urinary findings were unchanged. There was no evidence of increased postpartum bleeding. There was no maternal mortality, and following the standard of the American College of Surgeons the maternal morbidity was 2.6 per cent.

The odor of paraldehyde can be detected in both liquor amnii and maternal blood. It is likewise detectable on the breath of mother and baby for at least twenty-four hours. Fetal apnea was observed in six babies, all of whom began to breathe and cry as soon as mucus was removed from the larynx.

One baby died. This child was six weeks premature, weighed 2035 gm., and was delivered by low forceps and episiotomy after a seven-hour, five-minute labor.

TABLE II

	FIRST SERIES	SECOND SERIES	THIRD SERIES
Hours of labor (total)	16°34'	19°37'	13°20'
Primiparas	17°21'	19°56'	13°40'
Multiparas	10°45'	17°13'	12°23'
Before paraldehyde was given	11°32'	11°39'	7°54'
Primiparas	12°06'	11°55'	8°06'
Multiparas	7°35'	9°43'	7°07'
After last dose of paraldehyde	5°02'	4°41'	2°11'
Primiparas	5°15'	4°29'	2°42'
Multiparas	3°10'	6°10'	52'

There appeared to be a marked variation in the individual response to the emulsion. With some patients, a single dose, containing 15 c.c. of paraldehyde, was sufficient to give complete amnesia and excellent analgesia for several hours, while with others three doses had little or no effect in relieving pain or inducing forgetfulness. The larger and more obese patients reacted less favorably. Being readily soluble in oil, paraldehyde may be dissolved in the body fat and removed from the circulation. The occasional stimulation that occurs with the barbiturates was not observed in the second group of patients. Restlessness was seen only at the acme of the contraction, and the patient relaxed and dropped off to sleep again as the pain subsided.

The constant attention that these patients required to prevent injury to themselves and the difficulty of maintaining asepsis during delivery prompted the investigation of the effect of smaller doses in which it was the aim to have a conscious patient who rested well between contractions. It would be possible to apply such a technique to other than hospital confinements.

The results of this investigation indicate that in small doses paraldehyde is not an amnesic and only a fair analgesic, but is an excellent hypnotic. Patients who have received these small doses sleep or doze between pains but are wide-awake and in complete contact with their environment during the contraction. There is no danger of falling out of bed or breaking an arm over the side board. Such patients are much more quiet during the contraction, whimpering softly but never excited. When questioned following delivery, the response is characteristically the same: that the medication seemed to make the contractions stronger and more frequent and yet more bearable, and that between pains they fell asleep. In this series, labors were short and low forceps were employed in only 28 per cent, the other 72 per cent delivering spontaneously.

Paraldehyde appears equally suitable for use in primiparous and multiparous women. At the outset of this study, it seemed important carefully to individualize the patient with regard to parity, stage of cervical dilatation, strength and frequency of contractions, and condition of the membranes. On this basis, medication was withheld until the primiparous cervix had reached approximately 5 cm. dilata-

4. As far as is known, paraldehyde is absolutely safe to the parturient patient and fetus in the varying dosages used in this study.

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DISCUSSION

DR. RALPH A. REIS.—The advantage of paraldehyde is that with 4 c.c. doses we have kept the patients more quiet over longer periods of time than we have been able to do with either barbiturates or morphine. The objection we have had to barbiturates has been the necessity for constant nursing. This limits the use of barbiturates.

Paraldehyde is given early, repeated hourly, and the patient is quieted. We believe that by gradually increasing this minimum we will find the proper dose of paraldehyde for institution use and for the general practitioner who is conducting home deliveries. We think this will be an excellent method of keeping our patients under continuous sedation without producing any harmful effects on mother or fetus. We do not continue paraldehyde after ethylene analgesia has been started, although we have continued its use through a good part of the second stage.

DR. J. DUANE MILLER, GRAND RAPIDS, MICH.—I would like to ask some questions and I would like to report one death. Dr. DeCosta said the drug has a low toxicity, but just exactly how low is that toxicity? What is the variability in susceptibility to this drug?

Dr. Alexander M. Campbell and I within the past year, saw a patient in consultation who had been perfectly normal throughout her pregnancy. She went into labor spontaneously and was given a standard dose (6 drachms) of paraldehyde by rectum. She went into shock and the blood pressure went so low it could scarcely be taken. The patient lived approximately twenty-three hours; the fetus died shortly after the accident occurred. An autopsy was done which showed cloudy swelling of parenchymatous organs and blood destruction. It apparently was a death from the paraldehyde. It is said that the dose was checked carefully and was correct.

DR. C. E. GALLOWAY, EVANSTON.—This paper is based on 75 cases, 25 in each series. I would like to know what the experience has been with the continued, routine use of the drug.

We have given barbiturates in a little over 2200 cases, and the maternal mortality and fetal mortality have been increased. Before we can make any definite conclusion about any drug it must be used over a considerable period of time and in a considerable number of cases.

This whole question comes down to one point: in the particular labor that one is conducting, is it advisable to attempt to relieve the pain of labor? There

The mother, a primipara, received two 15 c.c. doses of paraldehyde in emulsion one hour apart, vomiting forty minutes after the first dose, and was delivered one hour, thirty minutes after the second. The baby died one hour after delivery and on postmortem examination a diagnosis of atelectasis was made.

TABLE III

	FIRST SERIES	SECOND SERIES	THIRD SERIES
Age			
Primiparas	22.7	24.1	20.3
Multiparas	32	28.7	28.0
Weight of patient			
Primiparas	148.6	142.9	146.7
Multiparas	130.7	147.3	155.6
Weight of fetus			
Primiparas	3290	3075	3273
Multiparas	3400	3708	3792
Fetal morbidity			
Tracheal catheter	1	3	0
Fetal mortality	0	1	0

DISCUSSION

Paraldehyde in large doses possesses both analgesic and amnesic properties. Large oral doses, however, are difficult to administer and frequently lead to vomiting. In addition, it causes a very definite percentage of restlessness and occasionally excitement at the acme of contraction. In smaller doses, paraldehyde is not an amnesic, and only a fair analgesic but is an excellent hypnotic and definitely seems to shorten the course of normal labor. Oral administration is highly desirable because it insures prompt and certain action. The unpleasant taste, smell and irritating effects can be avoided by the use of gelatin capsules. Paraldehyde is not advocated as a substitute for ethylene or ether, but as a valuable adjunct to either during the first and early second stages of labor. It is a stable, safe, inexpensive, readily procurable drug, requiring neither special equipment nor technique. In doses of 4 c.c. repeated at hourly intervals, special nursing is not necessary. With this dosage there is no increase in operative interference.

SUMMARY

1. The therapeutic value of paraldehyde given orally to patients in active labor has been investigated.
2. For convenience, these patients have been divided into three groups of twenty-five patients each; in each group the technique was varied.
3. Paraldehyde given in small doses of 4 c.c. every hour in gelatin capsules does not render the patient amnesic, is sometimes mildly analgesic, but is definitely sedative. In these doses it does not cause restlessness and seems to expedite delivery.

HEART DISEASE IN PREGNANCY*

AN ANALYSIS OF 110 CASES

ARTHUR E. LAMB, B.S., M.D., BROOKLYN, N. Y.

(From the Prenatal Cardiac Clinic and the Wards of the Brooklyn Hospital.)

THE functional classification for cardiac patients accepted by the American Heart Association was first applied to pregnant women with heart disease by H. E. B. Pardee¹ in 1922. Since the publication of this paper it has become generally accepted by most workers in this field as a guide in the ability of cardiac patients to withstand pregnancy and labor. Carr and Hamilton² in 1934 took exception to the use of the functional classification.

In 1934 a preliminary report³ was published from the prenatal cardiac clinic of The Brooklyn Hospital. In this report the functional classification for cardiac patients was used in evaluating pregnancy risks, and it was found that some of the women who would be considered excellent subjects for pregnancy and labor on the basis of this functional classification alone, stood the test of pregnancy badly. On account of this it was suggested that other factors should be considered.

This report is based on an analysis of the cases studied in the prenatal cardiac clinic and on the wards of The Brooklyn Hospital over a nine-year period from July, 1926, to July, 1935.

Since 1926, there has been a close cooperation between the obstetric and medical departments. A woman entering the obstetric clinic for prenatal care has her heart examined by the obstetrician on her first visit, and if the slightest abnormality is detected she is referred to the cardiac clinic where, after a careful history and a thorough physical examination of the heart, an electrocardiograph and an orthodiagram or a six-foot roentgen-ray are obtained. The forms of the New York Heart Association are used. This complete study is necessary to differentiate functional or adventitious murmurs from those of organic disease.

Functional murmurs are systolic in time and may be heard at any of the valvular areas. They are not associated with any change in size or contour of the heart. In addition there is no history of previous rheumatic infection. Women with these murmurs have been followed over this ten-year period and not a single instance of cardiac insufficiency developing during pregnancy or labor has been encountered. As noted in our preliminary report,³ a good proportion of these *bruits* disappear following delivery. A detailed analysis of this matter will be reported

*Read at the Scientific Meeting of the Committee of the Cardiac Clinic of the New York Heart Association, April 28, 1936, and before the Brooklyn Gynecological Society at The Brooklyn Hospital, October 2, 1936.

are plenty of cases in which one does not care to attempt it. When you decide that a case does need relief the question remains of what we are to use. I think we should attempt to work out this problem gradually and carefully.

DR. JOSEPH L. BAER.—A medicolegal angle is involved in the use of potent agents in the course of labor. You have heard why we have abandoned the routine use of the barbiturates. A woman subjected to certain drugs may become restless and sustain real injuries unless she is closely guarded and protected. The institution and the physician are responsible for that patient. That is why our superintendent, in discussion with our department, took the position that unless the patient is specially nursed she should not have a drug that might lead to serious trauma.

Special nursing is again a relative matter. The mere fact that a special nurse is engaged for a patient for eight hours does not necessarily mean that that special nurse is continuously at the bedside of that patient. It is conceivable that the special nurse may leave the patient for three minutes and in her absence something of serious moment happens to that patient. We have improvised side boards for our labor beds, but it has happened in our hospital that the patients have gotten over the side boards and out of bed, and it is readily understandable that this might result in a serious accident. Continuous special nursing must be really continuous to be adequate medicolegally.

DR. DeCOSTA (closing).—The only reference in the past decade to fatal termination was one by MacFall in the *British Medical Journal* in 1925, in which he reports a paraldehyde addict who committed suicide by drinking at least three ounces. He quotes two previous deaths of which he knew and they both occurred before 1900; one of these was a suicide, the other associated with typhoid fever.

So far as unusual susceptibility is concerned, we have not seen it in this small series. We have seen patients who were resistant to its action and one patient particularly, a doctor's wife, who received little or no benefit from 45 c.c.

We have run more than the 75 patients reported, but some were deleted from the present report, because they had received insufficient medication. There was also an additional series of twenty patients who received 6 c.c. of paraldehyde in capsules at hourly intervals and gr. $\frac{1}{6}$ morphine sulfate. The morphine usually accompanied the second dose of paraldehyde. This series was omitted because we were anxious to report the response to paraldehyde alone. With morphine there was better analgesia and amnesia and the advantages of small doses of paraldehyde were retained. At present we are employing this technique with satisfaction, and plan to discuss it in greater detail in a subsequent communication.

Waters, E. G.: Bleeding in Late Pregnancy, *Am. J. Surg.* 30: 444, 1935.

Placenta previa, ablatio placentae and rupture of the uterus constitute the most life-endangering causes of late pregnancy bleeding. The hemorrhage and/or shock associated produce profound alterations in the normal physiologic adjustment of the body. Depletion of blood volume and change of blood distribution are the primary factors in the development of the severe clinical conditions. Blood replacement by transfusion is an essential element in treatment. A series of cases occurring in 14,000 deliveries is reported.

J. THORNWELL WITHERSPOON.

TABLE III. VALVULAR LESIONS ENCOUNTERED IN RHEUMATIC HEART DISEASE

VALVULAR LESIONS	CASES	PERCENTAGE
Mitral insufficiency	13	12.7
Mitral stenosis with and without mitral insufficiency	76	74.5
Aortic insufficiency with mitral stenosis and insufficiency	10	9.8
Aortic stenosis and insufficiency with mitral stenosis and insufficiency	2	2.0
Tricuspid stenosis with mitral stenosis and insufficiency	1	1.0
Mitral valve involved in 100 per cent.		
Mitral stenosis with and without mitral insufficiency occurred in 89.		
Percentage—87		

fever was obtained; patients with a systolic murmur at the apex and a rheumatic history but with a normal cardiac silhouette were excluded. These rigid criteria should be fulfilled in order to avoid the inclusion of cases of functional systolic murmur.

On referring to Table IV, it is seen that no instance of decompensation was encountered with mitral insufficiency alone. There were 76 women who had definite mitral stenosis. Of the 106 pregnancies in these women heart failure occurred during 27 of them. Mitral stenosis was also found as the sole lesion in 5 out of 9 patients who died. Conclusions as to the incidence of failure and death in other lesions could not be drawn on account of the small number of cases. It is of the utmost im-

TABLE IV. RELATION OF VALVULAR LESIONS TO MORBIDITY AND MORTALITY

LESIONS	NO.	PREG-NANCIES	DECOMP.	PER CENT DECOMP.	DEATHS	
					TOTAL	PRENATAL CARE
Mitral insufficiency	13	15	0		0	0
Mitral stenosis with and without mitral insufficiency	76	106	27	25	5	2
Aortic insufficiency with mitral stenosis and insufficiency	10	13	3		2	0
Aortic stenosis and insufficiency with mitral stenosis and insufficiency	2	3	2		0	0
Tricuspid stenosis with mitral stenosis and insufficiency	1	1	0		0	0
Congenital pulmonary stenosis	3	4	3		1	1
Arteriosclerotic heart disease	3	3	1		1	0
Etiology unknown cardiac hypertrophy	2	5	0		0	0
Totals	110	150	36		9	3

Two cases not confined in The Brooklyn Hospital.

Decompensated	24.0%
Mortality	8.2%
Mortality of cases studied and treated in pre-natal cardiac clinic.	2.7%

in a separate paper. The recognition and separation of these cases from those presenting organic lesions is one of great importance for their inclusion in such study as this would so markedly reduce the heart failure and death rate as to give an entirely erroneous impression of the problem of pregnancy in the cardiac patient. As far as can be determined only patients suffering from organic disease of the heart are included in this report. Only those cases are accepted as having organic disease as determined by the criteria⁴ adopted by the New York Heart Association.

There were 110 cases of organic heart disease among the 5,366 admissions to the obstetric clinic from July, 1926, to July, 1935 (Table I). These were discovered

TABLE I. ANALYSIS OF PREGNANT CARDIAC CASES

Admitted to Obstetrical Clinic, July, 1926 to July, 1935	5366
Referred to Cardiac Clinic	367
Functional cardiac murmurs	257
Organic heart disease	110
Incidence of heart murmur in pregnant women	6.8%
Incidence of functional murmurs in pregnant women	4.8%
Incidence of organic heart disease in pregnant women	2.06%

among 367 patients referred to the cardiac clinic. The remainder, 257, had functional murmurs. The total incidence of heart murmurs in pregnant women was 6.8 per cent. Of these 4.8 per cent were of the functional type, 2.06 per cent represented organic disease. Sparks,⁵ from a survey of the literature up to 1929, reports an incidence of organic disease from 0.25 to 2.8 per cent. The more recent reports⁶⁻⁸ vary from 0.66 per cent to 4.15 per cent.

The 110 cases here reported were separated according to etiology (Table II); 102 were rheumatic, three were congenital, three were arteriosclerotic, while in two the

TABLE II. ORGANIC HEART DISEASE—ETIOLOGY

*Rheumatic	102
Congenital pulmonary stenosis	3
Arteriosclerotic	3
Etiology unknown cardiac hypertrophy	2
92.7 per cent of heart disease in pregnancy—rheumatic	

*In our preliminary report there was one case reported as syphilitic heart disease, and the finding of aortic insufficiency associated with a positive Wassermann during pregnancy. Subsequent negative Wassermann reactions and the finding of a presystolic murmur at the apex caused us to reclassify this case as rheumatic.

Since this paper was written, this patient died and autopsy revealed a syphilitic aortitis and aortic insufficiency. So the case should be reclassified as syphilitic disease of the heart, and consequently the incidence of rheumatic disease of the heart should be 91.8 per cent instead of 92.7 per cent.

etiology could not be determined. Of the heart disease encountered in this series 92.7 per cent was rheumatic. Carr and Hamilton² in a series of 500 patients report an incidence of 94.4 per cent. Among the rheumatic group, the valvular lesions encountered are shown on Table III. Mitral stenosis with or without mitral insufficiency was most frequent, occurring in 74.5 per cent. Carr and Hamilton² report the incidence of mitral stenosis to be 77 per cent; 80 per cent of their patients had mitral involvement while 100 per cent of this series had a mitral lesion. There were 13 women with mitral insufficiency. This diagnosis was made when a systolic murmur was found at the apex, together with definite changes in the size and contour of the heart on x-ray examination, and when a definite history of rheumatic

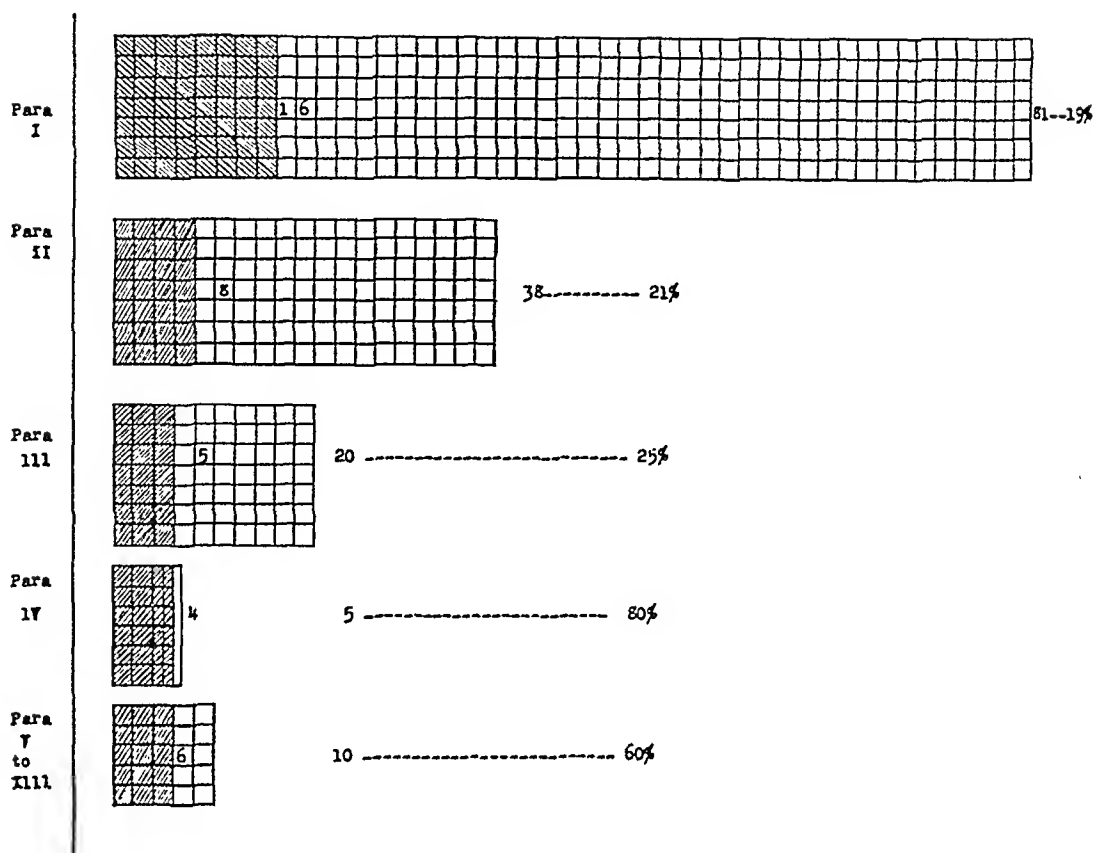


Fig. 2.—Relation of parity to decompensation; 154 pregnancies (4 pregnancies before admission to Cardiac Clinic). Two patients with arteriosclerotic heart disease did not decompensate, one para vii and one para xii.

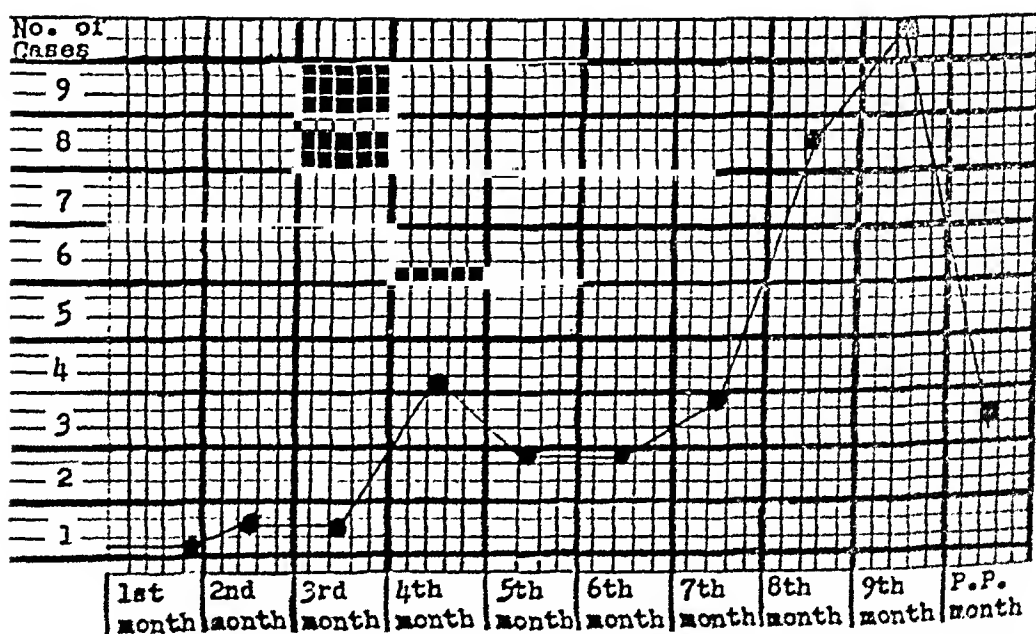


Fig. 3.—Rheumatic heart disease. Relation of months of pregnancy to decompensation.

portance, therefore, to differentiate between insufficiency and stenosis of the mitral valve because the former is a relatively benign lesion while the latter is an extremely grave complication of pregnancy.

The only congenital lesion encountered was pulmonary stenosis, and decompensation occurred in three of the four pregnancies.

Nine deaths occurred in this series of 110 patients, a total mortality of 8.2 per cent. Most of these deaths were in women who were admitted directly to the wards in acute decompensation and who had not been supervised in the cardiac clinic. There were only three deaths among the women who had had prenatal care, or a mortality of 2.7 per cent. In our preliminary report the mortality among patients treated in the cardiac clinic was 2.2 per cent, while in the untreated cases it was 20 per cent. The necessity of careful prenatal supervision is obvious.

It has been demonstrated by Carr and Hamilton² that there is a direct relation-ship between the age of the patient and the incidence of decompensation. Thirty-five per cent of their patients decompensated at the age of thirty-five. A chart (Fig. 1) has been prepared in which the patients in this series are grouped according to

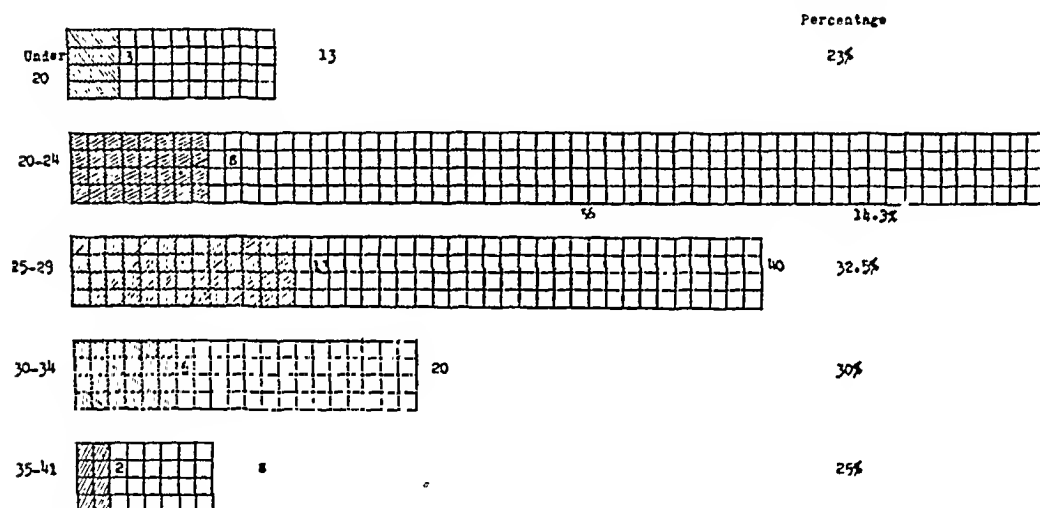


Fig. 1.—Rheumatic heart disease. Relation of age of patient to decompensation.

age. An increasing percentage of decompensation occurred up to the age of twenty-nine. The number of cases in the age group above twenty-nine years is small and an increasing percentage of failures cannot be shown.

The chart (Fig. 2) shows that there is an increasing percentage of failures with each subsequent pregnancy. Eighty per cent of the patients that returned for the fourth pregnancy developed signs of heart failure and of those that had over four pregnancies, 60 per cent failed. Two patients in this latter group had arteriosclerotic heart disease and did not decompensate, so actually there were 75 per cent of the rheumatic cases that failed. Therefore, 75 to 80 per cent of patients with rheumatic heart disease cannot tolerate more than three pregnancies.

In the preliminary report,³ a relationship between the month of pregnancy and the onset of decompensation could not be demonstrated, probably because the series was then small. In this study, as one would expect, the greatest number of decompensations occurred in the latter months of gestation (Fig. 3). As pregnancy advances there is a gradual increasing burden on the heart due to the increasing cardiac output. Stander⁹ has shown in normal gestation in animals and human

While the patients in this series were all classified functionally, they were not subjected to an exercise test. Reliance was placed on their ability to carry on the usual exertions and strains of life. If upon questioning there were no symptoms suggesting the slightest evidence of cardiac strain, they were placed in Class 1. The others were grouped accordingly. The number of patients in each functional group at the time of the examination is indicated in Table II. Eleven per cent of Class 1 patients, 10 per cent of Class 2A patients, and 69.2 per cent of Class 2B patients developed signs of cardiac insufficiency. The functional classification is therefore helpful in selecting pregnancy risks, so far as it indicates that women in Class 2B do not tolerate pregnancy well. If a patient is in Class 1 or Class 2A, it is no guarantee that she will pass through pregnancy and labor without development of cardiac insufficiency.

There are additional factors that must be considered to make a more accurate prognosis. These are:

- First: The structural changes in the heart. These have been judged by the size of the heart and the extent of the valvular damage.
- Second: The duration of the disease.
- Third: The presence of signs indicating activity of the rheumatic process.
- Fourth: The presence of auricular fibrillation.

1. *Structural Changes in the Heart.*—In 79 women the relationship of the total diameter of the heart to the transverse diameter of the chest has been studied. Table VI shows that the larger the heart in relation to the transverse diameter of the chest, the greater the danger of failure. Where the total diameter of the heart exceeded 55 per cent of the diameter of the chest, decompensation occurred in 50 per cent. When it was in excess of 60 per cent, 78 per cent failed, and when 65 per cent, they all decompensated. The larger the heart the greater danger of cardiac insufficiency.

TABLE VI. 79 CASES IN WHICH RELATIONSHIP OF SIZE OF HEART TO TRANSVERSE DIAMETER OF CHEST WAS OBTAINED

CARDIOTHORACIC RATIO	NO. OF CASES	DECOMP.	DIED	PER CENT DECOMP.
Less than 0.450	3	0	0	0
0.451-0.500	25	5	3	20%
0.501-0.550	21	5	0	24%
0.551-0.600	16	8	2	50%
0.601-0.650	9	7	4	78%
0.651-0.700	3	3	1	100%
0.701-0.750	2	2	1	100%
	79	30	11*	

* 2 patients died. One four years and one eight years following pregnancy. The other nine died during pregnancy.

beings that the cardiac output rises above the normal level early in the fourth month and steadily increases until at term it amounts to approximately 50 per cent above normal. This is of importance because if a patient decompensates early in pregnancy, the likelihood of another breakdown in the latter months of gestation is greater because of the increased cardiac strain existing at that time.

In most clinics today, the functional classification for cardiac patients accepted by the American Heart Association is used as an index of whether women with heart disease will be able to withstand the strain of pregnancy and labor. Cases are, therefore, grouped according to the ability of the heart to withstand effort, rather than according to the structural damage and other factors.

The following classification is used: Class 1, patients with organic heart disease able to carry on ordinary physical activity without discomfort. Class 2, patients with organic heart disease unable to carry on ordinary physical activity without discomfort: (A) activity slightly limited, and (B) activity greatly limited. Class 3, patients with organic heart disease and with symptoms or signs of heart failure at rest, unable to carry on any physical activity without discomfort. Pardee¹⁰ after studying the reaction of 106 pregnant cardiac patients to an exercise test concluded that Class 1 patients will not be expected to give trouble from cardiac insufficiency. Class 2A patients probably will not give trouble, but there is a fair chance that a Class 2B patient will decompensate. The Class 3 patients were not subjected to the test, as they were already decompensated, and he found their management difficult and the mortality high.

TABLE V. FUNCTIONAL CLASSIFICATION

LESION	NO. OF CASES	NO. OF PREGNANCIES	CLASS 1		CLASS 2A		CLASS 2B		CLASS 3	
			NO FAILURE	FAILURE	NO FAILURE	FAILURE	NO FAILURE	FAILURE	FAILURE	
Mitral insufficiency	13	15	7	0	8	0	0	0	0	
Mitral stenosis with and without M. I.	76	106	38	5	39	6	2	7	9	
Aortic insufficiency with M. S. and M. I.	10	13	3	0	6	1	1	1	1	
Aortic stenosis with M. S. and M. I.	2	3	0	0	1	0	0	0	2	
Tricuspid stenosis with M. S. and insufficiency	1	1	0	0	1	0	0	0	0	
Congenital pulmonary stenosis	3	4	0	1	1	0	0	0	2	
Arteriosclerotic heart disease	3	3	0	0	1	0	1	1	0	
Cardiac hypertrophy etiology unknown	2	5	0	0	5	0	0	0	0	
Total	110	150	48	6	62	7	4	9	14	Total
Number decompensated				6		7		9	14	36
Per cent decompensated				11%		10%		69.2%	100%	24%
Deaths				2				2	5	9

ciency developing during pregnancy is great. In order to examine the accuracy of these statements the patients in Class 1 and 2A that decompensated were analyzed according to the size of the heart and the presence of a long diastolic murmur at the apex. All but one of these patients showed either one or both of these signs (Table VIII).

TABLE VIII. ANALYSIS OF CLASS 1 AND 2A. PATIENTS THAT DECOMPENSATED ACCORDING TO EXTENT OF VALVULAR LESION

UNIT NO.	FUNCT. CLASS	SIZE OF HEART	LONG RUMBLING DIASTOLIC AT APEX	DIAG.
14416	1	0.594	No	M. S.
43101	1	0.457	Yes	M. S.
32506	1	0.635	No	M. S.
				M. I.
57675	1	0.591	Yes	M. S.
				M. I.
19162	1		Yes	M. S.
				M. I.
47837	2A	0.599	No	M. S.
12210	2A	0.500	No	M. S.
45272	2A	0.497	Yes	M. S.
34701	2A	0.537	Yes	M. S.
				M. I.
19360	2A	0.626	Yes	M. S.
				M. I.
51905	2A	0.584	Yes	M. S.
				M. I.
12282	2A	0.576	Yes	M. S.
				M. I.

Size of Heart less than 0.501—3 patients

Size of Heart from 0.501-0.550—1 patient

0.551-0.600—5 patients (Heart size above 0.551—7 or 63 per cent)

Number with long rumbling diastolic murmur 9 or 75 per cent.

There was only one patient in series who had neither a long rumbling diastolic murmur or heart size under 0.550 or 92 per cent showed with one or other sign.

TABLE IX. ACTIVE RHEUMATIC FEVER OR CHOREA DURING PREGNANCY

	NO. OF PATIENTS	NO. DECOMP.	DEATHS
Active rheumatic fever	4	2	0
Chorea	3	2	2
Ages of patients varied from 18-22 years with one exception age 35			
Rheumatic Cases		102	
Active Rheumatic Cases		7	
Percentage Activity		6.8%	

2. *The Duration of the Disease in Rheumatic Cases.*—There were 66 patients in whom a definite history of the onset of the rheumatic infection was obtained, and the duration of the disease was computed. Fig. 4 shows that in 10 patients who had rheumatic heart disease of less than five years' duration, 20 per cent decompensated. In this group we encountered patients with the signs of activity of the rheumatic process. This we will show later influenced the incidence of decompensation in this group. Twenty-six per cent failed who had

The extent of the valvular damage was determined by an analysis of the murmurs present. Table VII shows the relationship of the murmurs found to decompensation. None of the patients who presented only a systolic murmur at the apex gave trouble during pregnancy. Where a short presystolic or an early diastolic murmur occurred 15 per cent decompensated, but when in addition to the presystolic or early diastolic murmur, an aortic or tricuspid lesion was present, the number of failures rose to 28 per cent. A long rumbling diastolic murmur at the apex, existing throughout diastole, definitely increased the risk. Sixty-two per cent of these women decompensated. When this murmur was discovered, together with an aortic lesion, about the same percentage failed. The finding of this type of murmur at the apex is indicative of a high degree of structural damage of the mitral valve. Upon four of these patients postmortem examinations were secured, and they showed a high degree of mitral stenosis.

TABLE VII. RELATION OF ANATOMIC LESION TO DECOMPENSATION AND DEATH.
BASED ON ANALYSIS OF MURMURS

	NUMBER OF CASES	NUMBER OF DECOMP.	PER CENT OF DECOMP.	DEATHS	POST- MORTEM
Systolic at apex	13	0	0	0	
Presystolic or short diastolic at apex	45	7	15	3	
Presystolic or short dia- stolic at apex associated with aortic lesions and tricuspid	7	2	28	1	
Long diastolic at apex filling diastolic	32	20	62	8	4
Long diastolic associated with aortic lesion	5	3	60	1	
Totals	102	32		13	4

CASE 35173.—The heart was found to be normal in size. The mitral valve was stenotic, admitting the tip of only one finger.

CASE 15735.—The heart weighed 400 gm. Mitral valve markedly stenotic; does not admit the tip of the fifth finger. Mitral slit 1 cm. by 0.5 cm. in diameter.

CASE 57725.—The heart weighed 700 gm. The mitral valve admits the tip of one finger. The edges of cusps were rounded and thickened. The chordae tendinae were shortened, thickened, white, and fibrotic.

CASE 15005.—The heart was normal in size. The mitral orifice was funnel-shaped and narrow. The opening was about 4 by 7 mm. The valve cusps were thickened and coherent. The upper lobe of the right lung was completely consolidated. The left lung was moderately consolidated throughout. The patient died of lobar pneumonia.

There is a definite relationship between the extent of the structural damage in the heart and decompensation: no matter what the functional classification may be, if the size of the heart is more than 55 per cent of the total diameter of the chest or if the patient presents a long rumbling diastolic murmur at the apex the likelihood of cardiac insuffi-

TABLE X. AURICULAR FIBRILLATION

	NO. OF PATIENTS	DECOMP. NO. OF CASES		DEATHS NO. OF CASES	
		DURING PREG.	AFTER PREG.	DURING PREG.	AFTER PREG.
Rheum.	8	6	2	0	3
Arterio.	1	1	0	1	0
Time of decomp.		1 at 3 mo. 2 at 7 mo. 3 at 8 mo. 1—2 days P.P.	1—1 year P.P. 1—5 years P.P.		
Time of death				During labor	1—5 mo. PP. 1—1 yr. P.P. 1—5 yr. P.P.

Age of patients varied from twenty-three to thirty-nine years with one age nineteen. Duration of disease from onset of rheumatic fever to onset of auricular fibrillation eleven to twenty-three years.

Percentage of rheumatic cases with auricular fibrillation 7.8 per cent.

is not encountered more often in pregnancy may be because women in the childbearing ages are not as a rule old enough for the development of this irregularity. De Graff and Lingg¹¹ have shown that auricular fibrillation is usually a late manifestation in rheumatic heart disease as it was most commonly observed in the relatively long-standing cases. Auricular fibrillation is usually associated with heart failure. Of 8 cases in rheumatic women, 6 decompensated. The patients with auricular fibrillation with arteriosclerotic heart disease decompensated and died.

DISCUSSION

The problem of heart disease in pregnancy in this locality concerns itself nearly entirely with rheumatic heart disease. In this series 91.8 per cent of heart disease in pregnancy is rheumatic. The number of cases of heart disease due to other etiologic factors is too small to warrant any conclusions.

In this clinic when patients are first examined and the diagnosis of heart disease is completed, a decision is made as to whether, from a consideration of their history, physical findings and functional classification, they will be able to undergo the strain of pregnancy and childbirth. There were 10 women in the series who were judged unable to continue with their pregnancies. These pregnancies were interrupted for one or another of the following reasons: (1) A history of a previous cardiac decompensation. (2) The presence of auricular fibrillation. (3) Functional classification "2B." Class 1 and 2A patients were previously allowed to continue with pregnancy. As 11 per cent of Class 1 and 10 per cent of Class 2A patients decompensated during pregnancy, and two of Class 1 patients died, we realized that the criteria were not sufficient to safeguard the lives of these women and additional factors should be considered.

In addition to the criteria mentioned, the most important factor that should be considered is the extent of the structural damage in the heart

rheumatic heart disease of from six to ten years' duration decompensated. The number of instances of duration of disease exceeding twenty years is too small and no accurate conclusion can be drawn. Generally speaking, the longer the duration of the disease the greater the possibility of failure developing during pregnancy.

3. *Activity of Rheumatic Process.*—When women with rheumatic heart disease reach the childbearing age, most of them no longer present evidences of activity of the rheumatic process. Only 7 showed signs of acute rheumatic fever or chorea during pregnancy, an incidence of 6.8 per cent. Of the four with rheumatic fever, 2 decompensated with recovery, while of the 3 who had chorea 2 decompensated and died. It is interesting to note that these active manifestations of the disease occurred among the patients whose ages ranged from eight-

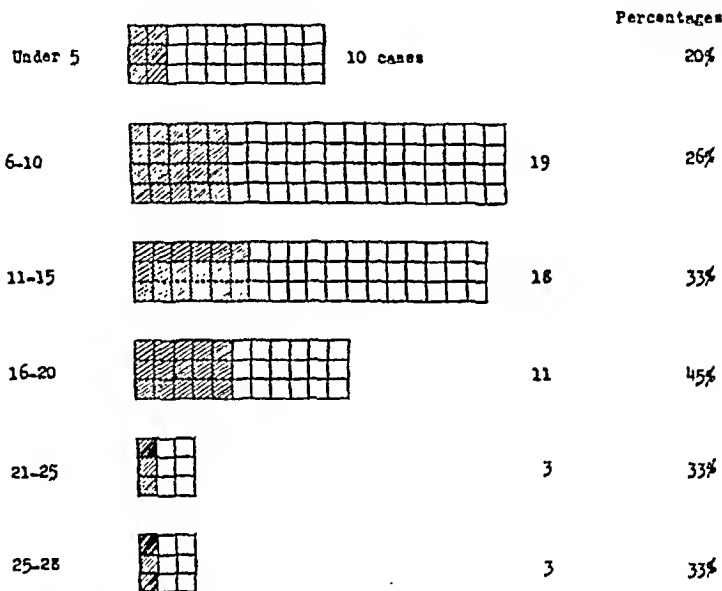


Fig. 4.—Relationship of duration of disease to decompensation. Sixty-six cases of rheumatic heart disease. History of onset of disease obtained. Note: One patient had chorea, first attack with pregnancy, and died. One patient with long-standing mitral lesion had rheumatic fever. Pregnancy and decompensation not included in above analysis.

een to twenty-two years of age, with one exception, a woman of thirty-five. It is important when examining these younger mothers to be alert for the signs of activity of rheumatic process. As decompensation occurs in over 50 per cent, it should be considered a serious complication of pregnancy (Table IX).

4. *Auricular Fibrillation.*—Auricular fibrillation occurred in 7.8 per cent of the rheumatic patients in this series. The ages of the patients who presented this arrhythmia varied from twenty-three to thirty-nine years with one exception, a girl of nineteen who also had signs of active rheumatism. The duration of the heart disease from onset of rheumatic fever to onset of auricular fibrillation varied from eleven to twenty-three years (Table X). The reason that auricular fibrillation

heart size of more than 55 per cent of the diameter of the chest, a long rumbling diastolic murmur at the apex, signs of active rheumatic infection and rheumatic heart disease of more than fifteen years' duration.

FOLLOW-UP

Seventy-eight women have been followed for a period extending from one month to nine years after delivery, 64 of these have been observed for over a year. Of these 78 women 6 died. One died suddenly following a recurrence of rheumatic carditis nine months following pregnancy. Another died five months after an interruption and sterilization. Death was due to cardiac decompensation. Another died two years and six months after last pregnancy with congestive heart failure. The fourth death occurred in a woman who had lived as a chronic invalid in this and the Montifiore Hospitals for four years and six months following her pregnancy. The fifth died four years and seven months after her confinement with a recurrence of rheumatic carditis and cardiac failure. The sixth died from lobar pneumonia six years and five months following her gestation. There are two patients still living who have developed auricular fibrillation since pregnancy and one who when last seen over three years after her last pregnancy was in acute decompensation. We do not believe that any conclusions can be drawn from the follow-up of our 78 patients as to whether they were worse following pregnancy. We are dealing with too many variables other than pregnancy that might influence the patients' condition. The natural progression of the rheumatic lesion alone would influence our conclusions in those that have been followed for a considerable period of time. In order to make any judgment as to the effect of pregnancy on the course of rheumatic heart disease a large number of patients must be followed from infection to death. The duration of the life and morbidity can be compared with a similar series of women who have never been pregnant. Only then will we be able to know definitely whether childbearing shortens the life span in women with rheumatic disease of the heart.

CONCLUSIONS

The use of the functional classification for cardiacs as the only guide, as to whether women undergoing pregnancy will be able to withstand the strain of gestation and labor, is not adequate. It has been demonstrated that other factors have to be considered, namely, the size of the heart, the presence of a long rumbling diastolic murmur at the apex in mitral stenosis, the presence of signs of rheumatic activity, the presence of auricular fibrillation and the duration of rheumatic heart disease.

Only if each case is individualized and all these factors considered can an accurate estimation of the risk entailed be obtained.

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This may be estimated by the size of the heart and the presence of a long diastolic murmur at the apex.

When the heart size is more than 55 per cent of the diameter of the chest, decompensation occurs in 50 per cent. When the heart size is in excess of 60 per cent, 78 per cent fail and when over 65 per cent all decompensated.

The finding of a long rumbling diastolic murmur at the apex is an ominous sign. It is associated with a high degree of stenosis of the mitral valve and when present decompensation occurs in 62 per cent. This sign was also elicited in 9 of the 13 women who have died since this series was started in 1926.

All of the twelve Class 1 and 2A patients that decompensated with one exception presented either one of these signs, namely, a heart size in excess of 55 per cent of the diameter of the chest or a long rumbling diastolic murmur at the apex. If the importance of these signs had been recognized at the time and the pregnancies interrupted, the decompensations might have been prevented. These signs are indications of advanced heart disease and women with these findings are very poor subjects for pregnancy, and careful contraception or sterilization should be seriously considered. This is of importance in clinic patients where there is great difficulty encountered in controlling them. Women will re-enter the clinic at the sixth or seventh month of gestation, pregnant again when every precaution has been advised for its prevention. If the indication exists for interruption of pregnancy, the indication exists for sterilization except perhaps in women with active manifestations of rheumatic disease.

It has been shown that over 50 per cent of the patients in this series that had active rheumatic infection failed during pregnancy. Although the number of instances of this complication was small, the indications from these findings suggest that it is dangerous and calls for prompt interruption of pregnancy. As these women are usually young and the changes in the heart may not be extensive, it is inadvisable to sterilize them, for they may be able to carry through a subsequent pregnancy.

The duration of the rheumatic disease is an important factor in prognosis. If the disease has been present for over fifteen years, the likelihood of extensive changes in the heart is great and decompensation will probably occur in about 45 per cent of the patients. However, it is not recommended that the duration of the disease itself be an indication for interruption unless there are other signs of extensive heart disease.

Auricular fibrillation is generally accepted as an indication for the interruption of pregnancy. In this series, decompensation occurred in 75 per cent. Therefore, in addition to a history of previous decompensation, auricular fibrillation and functional classification "2B" the following indications for the interruption of pregnancy should be added: A

As my mind goes back over an experience of thirty years, three significant changes in general attitude appear to me to signalize the increasing recognition of these facts. The first obstetric case which I ever "booked" in private practice was a young Irish woman in her first pregnancy, who complained, in her first or second interview, of an acute toothache. I advised her to see her dentist, and, if he thought necessary, to have the tooth extracted. The following day I was summarily dismissed from the case, because she and her mother never heard of any doctor advising a pregnant woman to have a tooth taken out.

Now, note that this family's reaction did not merely represent in that day a matter of lay ignorance, but was representative of an attitude shared alike by the medical and dental professions toward pregnancy. While it is true that the leading teachers in the obstetric field recognized the importance of dental infection and the necessity for its treatment in relation to pregnancy, the rank and file of both professions were reluctant to advise or undertake it.

Today in the Margaret Hague Maternity Hospital, the dental clinic sees about 4,500 cases a year, among which nearly half are referred to the exodontia clinic for extractions.

Our records show only one case of unfortunate outcome of this extensive practice.

E. C. (No. 27,198), a white, twenty-three-year-old primigravida, was admitted to the prenatal clinic, July 13, 1936. Sept. 17, 1936, she had the upper third left molar extracted in our clinic. She subsequently had several other acutely ulcerated teeth extracted by an outside practitioner. Three weeks later, Oct. 7, 1936, she was admitted to the Surgical Service of the Jersey City Medical Center with extensive purulent osteomyelitis of the mandible and cellulitis of the cheek and submaxillary area of streptococcal origin. Three drainage operations took place within the next month, the first under cycloidal anesthesia, the last two under gas oxygen. The day following the last operation she was transferred to us in labor nearly at term and delivered a healthy child under light ether. Four days later she developed extensive bronchopneumonia, subsequently empyema, and died on the fifteenth postpartum day.

This woman was pregnant; she had a tooth extracted; she died! But this sad history is not different from the occasional case seen in the nonpregnant; there was no deleterious effect on her pregnancy, due to the dental operations; and there is no likelihood that the occurrence of labor during her protracted septic illness predisposed to the fatal outcome, save in one lapse of art. The administration of inhalation anesthesia twice in twenty-four hours, once by the surgeons, and once by ourselves in the presence of a foul infection of the mouth, perhaps places responsibility for her death squarely on that mismanagement.

As long ago as the time of Paré, that omniscient genius who prophesied that there would probably be but little significant advancement in the knowledge and practice of surgery beyond that to which he had

DISCUSSION

DR. T. R. TURINO.—It is a generally accepted fact, that, with few exceptions, in medical or surgical complications of pregnancy our attention should be directed to the treatment of these conditions rather than the pregnancy. This axiom cannot be overemphasized in the management of the pregnant woman with heart disease. It is a problem which should be shared equally by the internist and the obstetrician. In the last five years at the Brooklyn Hospital, we have attempted to fulfill this requirement for care of the pregnant cardiac patient, in that the personnel of the prenatal cardiac clinic is made up of both cardiologists and obstetricians.

In a study of the obstetric aspect of heart disease in pregnancy made upon this group of patients, the following conclusions were drawn.

1. The average length of labor in the cardiac patient was not appreciably different from that in the noncardiac.
2. The incidence of operative interference was high, in order to shorten the second stage of labor.
3. Open drop ether was the anesthetic of choice for delivery.
4. The average weight of the babies born to cardiac mothers was slightly above the average normal.
5. The incidence of spontaneous premature labors was slightly higher.
6. There were 23.6 per cent of the patients in this series who decompensated either in pregnancy or during labor.
7. The uncorrected fetal mortality was 10.4 per cent.
8. Eight mothers died, an uncorrected incidence of 7 per cent. Five of these patients had no prenatal care.
9. The pregnant cardiac patient is best managed through pregnancy and labor by the joint efforts of the internist and obstetrician.

SURGICAL COMPLICATIONS OF PREGNANCY*

S. A. COSGROVE, M.D., F.A.C.S., JERSEY CITY, N. J.

(From the Margaret Hague Maternity Hospital)

NO ONE realizes more thoroughly than the trained obstetrician the profound changes in the maternal organism entailed by pregnancy. He is also thoroughly alive to the interaction between pregnancy and any intercurrent medical or surgical condition from which the mother may suffer. He knows that the prognosis of the pregnancy may be profoundly influenced by the intercurrent condition, and that the course and progress of the intercurrent disease may be very seriously affected by the strain of pregnancy.

But he recognizes also two other considerations: First, the tremendous capacity of the maternal organism for accommodating itself even to double strains of a serious nature; second, that the natural course and termination of the pregnancy in general terms represents less strain and less chance of disaster than does artificial interference with that course and termination.

*Read (by invitation) before the Obstetrical Society of Philadelphia, January 7, 1937.

nancy should, in general, be thought of, and managed, just as though the pregnancy did *not* exist, and the pregnancy itself should *not* be interfered with because of the simultaneous occurrence of such diseases.

I had supposed that this statement did actually represent almost universal opinion and practice, until one of my students challenged me by saying that one of his teachers did not think as I did in relation to appendicitis. Thus challenged, I reviewed the expression of several recent writers relative to this particular condition.

The opinions of authors of recent obstetric texts are quite unanimously in line with noninterference, although DeLee implies the occasional advisability of Porro section in relation to appendicitis in late pregnancy.

To quote rather fully from the 1933 edition of DeLee, he says that the greater seriousness of the results and prognosis of appendicitis, particularly in late pregnancy, depends on:

1. The fact that protective adhesions do not form so well because of dislocation of relation of the appendix, the gut and the omentum by the uterus.
2. Inflammatory processes tend to be more acute because of increased general vascularity of the pelvic abdomen.
3. Because of the same factor, thrombosis and phlebitis tend to occur more frequently.
4. Because of the upward dislocation of the appendix, suppuration, when it occurs, involves the higher and less resistant portions of the peritoneum.
5. Because of the occupancy of the greater part of the abdominal cavity by the uterus, drainage of pus is less facile and it tends to burrow more extensively.
6. Because of the distention of the abdomen by the uterus the occurrence of intestinal distention in connection with the appendicitis itself, and operative procedure undertaken in its treatment causes more embarrassment of respiration, and more frequent pulmonary complications.
7. For the same reason intestinal obstructive symptoms are more frequent and occur earlier.
8. There is considerable risk of bacterial infection of the placental site.

Many other authors recognize the validity of these modifying factors represented by pregnancy.

DeLee further says: "All of these considerations combine to cause a very high mortality after labor occurs as the contractions of the uterus may rupture the appendix itself, or the walls of an abscess cavity, particularly in the third stage and puerperium. The mortality in appendicitis complicating late pregnancy or labor is 40 per cent. In regard to the operative management, however, he says:

"The uterus is manipulated as little as possible, ... 'Get in and get out quickly' ... " and states further that cesarean section is contra-indicated.

Beck in his *Obstetrical Practice*, published in 1935, says: "In reference to operative treatment of appendicitis in late pregnancy, handling of the uterus ... is to be avoided as much as possible ..., and makes no reference at all to direct operative interference with pregnancy as part of the surgical treatment of the complication.

Schumann, in his *Textbook on Obstetrics*, in 1936, says of the operative treatment of appendicitis, that hysterotomy should never be attempted.

Stander, in the 1936 edition of *Williams Obstetrics*, mentions the suggestion of some authorities to perform cesarean section at the same time as operating for appendicitis, but expresses his firm conviction that this procedure will generally increase the gravity of the situation.

himself attained, down to the time that McPheeters wrote his very significant monograph in 1929, there had been an almost universal consensus that varicose veins in pregnancy were not susceptible to any except expectant treatment. In our own prenatal clinic we have so far given 3,445 injections for varicosities to 695 patients. Most of these have been in the lower extremities, but we have not hesitated to inject varicosities of the vulva and of the vagina. To the best of my knowledge, hospitalization for complications following this type of treatment has been necessary in only one case where a rather extensive slough developed over the site of injection, and one case of extensive severe cellulitis of the thigh and leg.

The textbook I used as a student was the then new, elaborate and very modern first edition of J. Clifton Edgar's *The Practice of Obstetrics*.

Dr. Edgar says of the "Curative treatment" of eclampsia, i.e., after the onset of convulsions, "empty the uterus under deep anesthesia by some method that is rapid and that will cause as little injury to the patient as possible." "Many cases that could...be saved will probably succumb if...the teachings are followed...that the eclamptic uterus should not be disturbed...." "...There is scarcely an authority of the present day who absolutely rejects local interference...." "...The best authorities are in favor of emptying the uterus as quickly as possible." "Expectant...treatment will almost surely be followed by the death of the child and about one-third of the mothers...." "But if the uterus is promptly evacuated by suitable surgical means...the mother is practically subjected to no danger." "The popular method of the present day seems to be mechanical dilatation of the cervix and prompt extraction of the fetus. This method is safe and effective when properly performed." Yet he states that it will often take an hour and a half (under deep anesthesia!) and dilates on its many difficulties and dangers.

The almost complete unanimity of opinion at the present time in substituting entirely expectant treatment of the eclamptic mother for this universal interference so insisted upon by the leading authorities of scarcely more than a quarter of a century ago, represents perhaps the most significant improvement of obstetric practice during that period.

Similar conservative tendencies in the last few years have seemed to be more or less realized in relation to other complications, such as cardiac diseases and tuberculosis. I am inclined to think that the feverish furore to utilize so-called therapeutic abortion in the presence of hypertensive and nephritic toxemias, now noticeably rampant in some clinics, will presently give way to a saner and more balanced management of these cases.

The change in ideas of management of the three frequent and important complications of pregnancy, which I have alluded to, has seemed to me to exemplify a change of thought toward all complications of pregnancy.

The end-result of such general change might then be expressed as follows: The other diseases which may occur concomitantly with preg-

permits the operator to determine the degree of soiling after the uterus has contracted, and make a more definite and permanent toilet of the abdomen."

Paul Titus quotes, and apparently concurs with Marbury in favor of hysterotomy, and, in the presence of peritonitis, hysterectomy.

B. C. Hirst has been repeatedly quoted as in favor of hysterotomy in the presence of generalized peritonitis.

Wilson says with reference to appendiceal abscess in late pregnancy, "...labor will follow operation within a few days with disastrous results...the uterus should be emptied at the time of operation in the interest of both mother and child." "If a marked peritonitis is present...a rapid Porro operation is the safest procedure...." "The two-flap, low section...ranks next to the Porro operation for safety, whenever it can be properly performed. The classical section, because of its simplicity, is the method best adapted for most cases and...will yield good results....In the last trimester...cesarean section, followed by appendicectomy, is advocated as the procedure which will give the best results."

King suggests emptying the uterus before performing appendicectomy, to reduce its size and facilitate the latter operation.

Rose says the consensus is, that in the presence of rupture and localized or spreading pus infection late in pregnancy, it is best to remove the appendix and do a Porro section.

Schmid, Puppel, La Jemtel are among others who concur in this alleged consensus.

This brief review of opinion shows that in early pregnancy there is complete agreement as to the wisdom of noninterference with pregnancy in the presence of acute appendicitis and its sequelae. But where the latter condition complicates the last two months of gestation, and especially when labor is imminent or actually in progress, there is sharp divergence of practice.

It seems to me that acute appendicitis is a sufficiently frequent and certainly serious enough complication of late pregnancy to have our practice standardized.

I would therefore invite your attention to the following cases of surgical complications of pregnancy occurring in our own clinic. It will be observed that they do not include:

a. Cases in which the surgical indication is purely obstetric, as ectopic gestation, rupture of the uterus, mechanical dystocia, abruptio placentae.

b. Cases which by their nature necessarily involve sacrifice of the gestation, as fibroids incompatible with continued evolution of pregnancy, or carcinomata uteri.

c. Cases where, in a dying mother, antemortem section is done wholly in the interest of a living fetus.

COMMENT

These cases fall into three groups: First, cases of appendicitis in the first seven months of gestation, in which all the mothers survived, as did all but three of the babies, the causes of these deaths being eventually discussed. As previously indicated, this group does not fall into

When wider reference to published opinion is made, however, the conservative expressions of the authors quoted is not found to be unanimously endorsed with reference to those cases occurring late in pregnancy, or in labor.

Among those who concur with conservative practice are Norton and Connell, of our staff, who recently reviewed eight cases from our own service, and who conclude: "Acute appendicitis with peritonitis complicating labor, should be managed surgically as it is at any other time, and the labor allowed to continue with delivery through the birth canal, in the absence of an indication requiring a different obstetrical procedure."

Maes stresses the importance of prompt surgical intervention in appendicitis complicating pregnancy, but says "...the gravid uterus should be handled as little as possible," and emphatically denounces as pernicious and unwarranted any operative interference with the pregnancy at the same time.

McDonald says that "...an acute abdomen with probable peritonitis is an unfavorable field for hysterotomy," and that radical termination of pregnancy will not at all relieve the load of sepsis and impending labor; that "hysterotomy ... is a desperate procedure for a condition already nearly hopeless.... Abdominal section is... only too popular. ... For the condition under consideration it has a number of overwhelming contra-indications," among which are:

1. There is great danger of directly infecting the uterus.
2. The uterus may not heal well, and may rupture in subsequent pregnancies.
3. It is obstetrically objectionable in young women with no permanent dystocia.

He concludes, "I can find no justification for abdominal hysterotomy unless labor is imminent, and there is actual dystocia which prevents vaginal delivery."

Robert A. Kimbrough of Philadelphia in a personal communication states that he is quite in accord with a wholly conservative attitude.

Krauss, Barber and Miller, Portes and Sequy, among others support this view.

Many authors take a somewhat modified stand, which is fairly representatively expressed by Heineck, who says that it may be necessary to resort to vaginal or abdominal cesarean section where coexistence of obstetric complications such as definite pelvic contracture or placenta previa requires unusual methods.

But there is a not inconsiderable number of writers who are so obsessed with the danger of labor activity on the course and outcome of concurrent appendicitis, that in late pregnancy they do not hesitate to advise termination by:

1. Vaginal delivery before opening the abdomen to treat the appendicitis, even to the extent of employing forcible dilatation of the cervix, or vaginal cesarean section.
2. Abdominal hysterotomy at the same time that the appendix is dealt with.
3. Removal of the uterus at the same time as appendicectomy is done.

Thus Maes quotes Cooke and Mason "complacently mentioning" accouchement forcé in multiparas in expert obstetric hands.

He also quotes DeLee as believing low cervical section safe if the patient is in labor, but we have already seen that DeLee in later writings does not advise this procedure.

Marbury says: "... it may be wiser to make a paramedian incision and empty the uterus by cesarean section first, and deal with the appendix secondarily. This

TABLE II

IDENTITY ADM. DATE	DIAGNOSIS AND OPERATION	OUTCOME OF PREGNANCY	MORTALITY	
			M	B
11. J.B. 8404 2/13/33	Normal pregnancy Ac. purulent appendicitis, 8th mo. Appendicectomy	Premature parturition 3rd p.o. day	L	L
	Difficult delivery of appendix from retrocecal bed—Postoperative course was completely afebrile; early parturition <i>did not</i> disturb it.			
12. T.D. 8382 4/12/33	Normal pregnancy Ac. purulent appendicitis local peritonitis, 9th mo. Appendicectomy Drainage	Normal parturition Term, 15 p.o. day	L	L
	One day febrile morbidity, except for mammary abscess on 21st p.o., 6th p.p. day; delivery was <i>not</i> precipitated by operation; smooth postoperative convalescence was <i>not</i> modified by delivery.			
13. M.M. 4867 9/3/34	Normal pregnancy Ac. purulent appendicitis 9th mo. Appendicectomy	Normal parturition Term, 22 days p.o.	L	L
	One day p.o. febrile morbidity; operation <i>did not</i> precipitate delivery			
14. J.H. 19680 12/20/34	Normal pregnancy Ruptured gangrenous appendicitis with twisted pedicle cyst of ovary and peritonitis, <i>intrapartum</i> Appendicectomy and drainage	Normal parturition (low forceps to expedite) 1 day p.o.	L	L
	This case reported in detail by Norton and Connell; actual labor had begun before operation. Operation <i>did not</i> essentially modify course of labor; labor <i>did not</i> modify smooth p.o. convalescence.			
15. E.T. 20669 1/3/35	Normal pregnancy Subacute appendicitis, 8th mo. Appendicectomy	Normal parturition Term (low forceps to expedite)	L	L
16. M.D. 23958 8/27/35	Normal pregnancy Ac. perforated appendicitis with general peritonitis, 8th mo. Appendicectomy, drainage Secondary drainage Laparotomy; enterostomy	Spontaneous premature delivery, 10 days p.o.	D	L
	Patient admitted 2 days after onset, with repeated purgation during that interval, and with extensive generalized peritonitis. Immediate prognosis was most grave, and course so unsatisfactory that secondary drainage operation was performed <i>before</i> labor had occurred, and could be assessed as a factor of disturbance. Fatal outcome believed to depend on delayed diagnosis and early mismanagement, and to be expected even had patient <i>not</i> been pregnant. Further believed that augmentation of original operative shock by <i>any</i> method of emptying uterus at that time would have been fatal.			

TABLE I

IDENTITY ADM. DATE	DIAGNOSIS AND OPERATION	OUTCOME OF PREGNANCY	MORTALITY	
			M	B
1. V.D. 12726 4/18/33	Normal pregnancy Ac. gangrenous appendicitis, 6th mo. appendicectomy, drainage	Normal parturition. Term	L	L
2. F.S. 13229 4/21/33	Nephritic toxemia, pregnancy Missed abortion, 4th mo. Ac. gangrenous appendicitis, 7th mo. Appendicectomy No p.o. morbidity; death of baby not related to appendicitis; abortion did not disturb course.	Spontaneous extrusion conception product 3rd p.o. day	L	D
3. A.K. 13604 5/9/34	Normal pregnancy Ac. gangrenous appendicitis, 5th mo. Appendicectomy	Parturition normal Term	L	L
4. E.H. 16179 2/18/34	Normal pregnancy Ac. purulent appendicitis, 6th mo. Appendicectomy	Normal parturition Term	L	L
5. H.O'B. 17672 4/31/34	Normal pregnancy Ac. ulcerative appendicitis, 5th mo. Appendicectomy	Normal parturition Term	L	L
6. R.G. 18904 8/12/34	Normal pregnancy Ac. gangrenous appendicitis, 2nd mo. Appendicectomy	Normal parturition Term	L	L
7. M.B. 22480 5/17/35	Normal pregnancy Ac. ulcerative appendicitis, subac. bilateral salpingitis, 3rd mo. Appendicectomy Salpingectomy	Normal parturition Term	L	L
8. H.E. 993 11/23/35	Abnormal pregnancy Cornual implantation, threatened abortion Ac. catarrhal appendicitis, 3rd mo. Appendicectomy Death of baby dependent on abnormal implantation; operation did not hasten outcome.	Spontaneous complete abortion 28 days p.o.	L	D
9. M.N. 25259 12/29/35	Normal pregnancy Recurrent ac. ulcerative ap- pendicitis, 3rd mo. Large lutein cyst left ovary Appendicectomy Oophorectomy Fetal death due ovarian pathology and removal; abortion did not disturb afebrile course.	Aborted spontaneously completely, 6th p.o. day	L	D
10. A.O'C. 25872 2/20/36	Normal pregnancy Ac. catarrhal appendicitis Multilocular intraligamentous cystadenoma of ovary, 3rd mo. Appendicectomy Extirpation of cyst.	Normal parturition Term	L	L

This accommodation is so usual a part of the natural history of all intraabdominal inflammatory states in relation to the natural functioning of all the viscera, that undue alarm concerning the equally natural functioning of the uterus is hardly warranted.

So also the fear that "labor will follow operation within a few days with disastrous results" is not substantiated in our experience, as several of our cases have delivered in from a few hours to several days without such disaster.

On the other hand, it does not seem to us tenable that the emptying of the uterus by any of the proposed interfering procedures can in any possible way be "in the interest of" the mother. The opening of the highly vulnerable genital tract to the direct invasion from contiguous

TABLE III

IDENTITY ADM. DATE	DIAGNOSIS AND OPERATION	OUTCOME OF PREGNANCY	MORTALITY	
			M	B
19. M.F. 16823 1/29/34	Normal pregnancy Twisted pedicle ovarian cyst 3rd mo. Oophorectomy	Normal parturition Term	L	L
20. G.R. 12472 6/23/34	Normal pregnancy Twisted pedicle lutein cyst of ovary, 3rd mo. Oophorectomy Fetal death probably due to nature of pathology	Incomplete abortion 11 days p.o. Digital extraction secundines	L	D
21. E.S. 21686	Normal pregnancy Pedunculated fibroid Ac. hemorrhagic degenera- tion, 4th mo. Resection of tumor involving myometrium of fundus As is not infrequently observed, even incision into the substance of the pregnant uterus itself may not disturb the pregnancy, nor result in dangerous weakening of the wall thereof.	Parturition normal Term	L	L
22. A.G. 24139 9/16/35	Normal pregnancy Ac. hemorrhagic pancreatitis; general peritonitis, 7th mo. Exploratory laparotomy, drainage. Patient admitted 2 days after onset of acute symptoms, with back- ground of acute alcoholism and severe abdominal trauma—symptom picture was confusing. The acute surgical condition with its severe toxicity doubtless caused fetal death and precipitated delivery. The upper abdominal exploration can hardly be held to have done so. The parturition almost certainly did not malignly affect the already hopeless con- dition of the patient.	Spontaneous premature delivery (elective low forceps to expedite) 15 hours p.o.	D	D
23. H.B. 20673 12/6/34	Normal pregnancy Adenocarcinoma of ovary, 6th mo. Salpingo-oophorectomy Subsequent to operation there was a series of intensive deep x-ray exposure. This may have induced premature labor. The operative interference per se could scarcely have done so, as more than a month had elapsed following it. At present, 2 years later, mother and babe are in apparent good health.	Spontaneous premature delivery, 32 weeks, 33rd p.o. day	L	L

TABLE II—CONT'D

IDENTITY ADM. DATE	DIAGNOSIS AND OPERATION	OUTCOME OF PREGNANCY	MORTALITY	
			M	B
17. H.K. 26461 8/20/38	Normal pregnancy, term Ac. purulent appendicitis Appendicectomy, drainage Local purulent peritonitis present; appendix was exposed with much difficulty; only 2 days p.o. febrile morbidity. Labor did <i>not</i> modify the good postoperative course.	Normal parturition 24 hours p.o.	L	L
18. H.M. 28154 10/27/36	Normal pregnancy, term in labor Ac. purulent appendicitis in- trapartum Appendicectomy, intrapartum Active labor commenced at least two hours before operation, and perhaps earlier, as it was hard to distinguish labor contraction in the presence of the severe inflammatory pain, so that operation did not initiate labor, nor modify its normal evolution. Neither did labor modify a smooth postoperative course, marked by only 2 days' febrile morbidity.	Normal parturition 24 hours p.o.	L	L

the field of controversy, as all commentators agree that no disturbance of pregnancy is necessary thus early in pregnancy.

Second: cases of acute appendicitis occurring in the eighth and ninth months of pregnancy, two of them intrapartum. One mother died, but all the babies survived. There is some detailed discussion of each of these cases.

Eight of the cases in these two groups have been previously reported by Norton and Connell.

Third: a small group of miscellaneous intraabdominal surgical complications, each of which is discussed. One mother and two babies died.

In reviewing the case discussions, our experience would not appear to lend much support to several of the factors of fear in relation to appendicitis in late pregnancy included in the opinion of DeLee and others already quoted. Certain of them appear theoretical rather than based on factual observations. Thus, in our several cases of ruptured appendix with peritonitis, drainage appeared to be just as effective, and postoperative course just as smooth, as it could reasonably be expected to be in the nonpregnant. Our mortality, even in the severe cases late in pregnancy, does not approach the high percentage quoted by DeLee.

The theoretic risk of infection of the undisturbed placental site is not, in our opinion, nearly so real as the actual risk of infecting the site should the uterus be opened transperitoneally, nor of infecting the broad lymphatic and cellular tissue areas exposed in extirpating the uterus.

The fear of tearing the appendix or adhesions would appear to overlook the extreme mobility of all the abdominal viscera, and the possibility thereby of mutual accommodation to shifting relationship in spite of extensive inflammatory adhesions.

THE MORTALITY AND COMPLICATIONS OF 3,129 SUPRACERVICAL HYSTEROMYOMECTOMIES*

HERBERT E. SCHMITZ, B.S., M.D., F.A.C.S., CHICAGO, ILL.

A DISCUSSION of the advantages and disadvantages of total versus subtotal hysterectomy has usually resulted in the expression of a divergence of opinion. Such reports were usually based on the good end-results of patients treated by the reporting surgeon in his service at the hospital. Depending on skill and experience the reports depicted the surgeon's mastery of either one of the techniques but did not settle the question of the fate of the patient after the operation, if subjected to a total or subtotal hysterectomy. This study was prompted by the belief that a complete analysis of a large series of cases, performed by a group of gynecologists in a charity hospital, would give more definite data. The cases here presented comprise all the supravaginal hysterectomies performed at the Cook County Hospital for myomas of the uterus during a ten-year period and listed as such in the hospital record room. The study comprises a review of the records during the ten years from 1926 to 1936.

Dixon¹ considers myoma the most frequent tumor in the human body and quotes Bland as saying that 20 per cent of all women have fibromyomas after the age of thirty-five. Davis and Cusick,² in a critical study of 335 hysterectomies, conclude that hysterectomy is the operation of choice for fibromyomas of the uterus. It was done in approximately 72 per cent of their series. The same percentage of hysterectomies for myomas also prevailed in the clinics of 45 of our leading operators in this country and Canada.

This report considers the type of patients, the associated pathology, the postoperative complications, and the mortality of supravaginal hysterectomies performed at the Cook County Hospital during the past ten years.

TYPES OF PATIENTS

County charity hospitals accepting all patients that apply for treatment receive many far-advanced and neglected cases. Operations oftentimes are deferred for days in an attempt to build up the patient's general condition by bed rest, proper food, care of the bowels, removal of foci of infection, and in severe secondary anemias by transfusion of whole blood.

About half of all the patients on the gynecologic service are negroes, and many of them, as well as a fair number of white women, have a four-plus Kahn or Wassermann reaction. There is a high incidence of pelvic infection among these patients, thus adding to the operative

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dangerously inflamed tissue is alike poor obstetrics and poor surgery. Hardly less defensible is the breaking down of natural peritoneal barriers by the extensive dissection involved in hysterectomy.

It may here be objected that only one of our cases actually had a full-blown general peritonitis; that she died; and that it is particularly in this type of case that radical measures are advised. Others of our cases, however, have been ruptured and have had at least beginning peritonitis, thereby falling into the group of most serious potentiality. And in this connection I believe it generally sound, that the sicker the patient, the more essential it is to limit surgery to the absolute minimum consistent with extirpation of the focus of trouble and adequate provision of drainage. Beyond that, the natural resistance of the patient and the uninterfered-with maintenance of all her normal functions offer the best prognosis.

Based then on the 23 cases of acute abdominal surgical necessity occurring in 25,000 living births, I would state as justifiable conclusions:

1. Acute appendicitis is a surgical condition invariably calling for prompt operative intervention.

2. This indication is not modified, but is even more promptly imperative when appendicitis complicates pregnancy, even at or near its termination.

3. Its surgical treatment should *not* be combined with any manipulation to terminate pregnancy. This statement may be modified only by:

- a. The legitimacy of simple procedure to expedite termination of the second stage of spontaneous labor;

- b. Recognition of the very rare possibility of concurrent serious factors of obstetric dystocia. When this occurs, recourse may be necessary to delivery by the abdominal route. But such interference should be reserved until after the onset of spontaneous labor, and an extraperitoneal approach selected.

4. The same principle applies in other surgical complications of pregnancy.

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nosed during operation are filed in the hospital records as malignancies and not under the group of myomas. The four cases were unrecognized grossly and filed under myomas before the pathologic diagnosis was returned.

POSTOPERATIVE COMPLICATIONS

There were 182 or 5.8 per cent postoperative complications. The criteria for morbidity were the necessity for remaining in the hospital more than four days beyond the average stay of ten days or a temperature over 101°. The high incidence of pelvic infections present in these cases at the time of operation is most likely the responsible factor in the production of wound infection.

TABLE II. POSTOPERATIVE COMPLICATIONS

Wound sepsis	126	Fecal fistula	1
Postoperative pneumonia	9	Parametritis	1
Localized peritonitis	8	Psychosis	1
Pelvic cellulitis and abscess	8	Acute pharyngitis	1
Vaginal hemorrhage	7	Central nervous system syphilis	1
Secondary wound suture	4	Accidental tear of bladder	1
Thrombophlebitis	3	Erysipelas of back	1
Cystitis	3	Auricular fibrillation	1
Evisceration	2	Diabetes mellitus	1
Hematoma of wound	1	Vesicovaginal fistula	1
Bleeding from wound			1

Burch and Burch³ in reporting a series of 200 hysterectomies performed at Vanderbilt University Hospital, list the complications of the fibromyoma cases and those of pelvic inflammations. The incidence of wound infection in the fibroid group was 9.1 per cent while in the latter group it was 23.2 per cent. Table II lists all the postoperative complications.

Table III gives the morbidity in 1,159 cases of supravaginal hysterectomy performed for myomas and reported by Read and Bell.⁴

TABLE III. MORBIDITY TABLE OF READ AND BELL

Unknown	138	7.9%	Secondary hemorrhage	5
Wound sepsis	52	3.0%	Malignant cachexia	5
Pulmonary complications	35	2.0%	Tonsillitis	4
Femoral thrombosis	35	2.0%	General peritonitis	2
Urinary infection	28	1.6%	Acute dilatation of stomach	2
Septic case	17	1.0%	Parotitis	2
Ruptured abd. wound	12	0.7%	Broad ligament hematoma	2
Wound hematoma	9	0.5%	Auricular fibrillation	1
Parametritis	5	0.3%	Septicemia	1
Intestinal Obstruction				1

The morbidity in this series amounts to 20.6 per cent; however, the authors mention that of the 138 unknown cases many were detained in the hospital because of improper home facilities or other unimportant causes.

risk. The seven regular attending gynecologists performed most of the operations but a few were done by the general surgeons, by associates and by senior internes under the direct supervision of the senior attending gynecologists.

ASSOCIATED PATHOLOGY

Of the 3,129 cases reviewed, 1,323 or 42 per cent had associated pathology complicating the myoma. Chronic salpingitis was by far the most frequent complication, being present in 834 cases or 26 per cent. Other types of inflammatory conditions were present in 1,185 or 38 per cent of the cases. Tubo-ovarian abscess, pyosalpinx, pelvic abscess, and chronic pelvic peritonitis composed the other 351 infections. Table I shows the complete list of all the associated pathologic conditions listed in the order of their frequency. Both the operative and pathologic reports were studied for this information.

TABLE I. ASSOCIATED PATHOLOGY IN ALL CASES

Chronic salpingitis	834	Pelvic endometriosis	1
Hydrosalpinx	118	Chondroma	1
Tubo-ovarian abscess	100	Sarcoma	1
Pyosalpinx	65	Anaplastic squamous cell carcinoma	
Chronic pelvic peritonitis	61	of ovary	1
Degenerated myoma	35	Brenner tumor	1
Intraligamentous myoma	20	Gärtner's duct cyst	1
Dermoid cysts of the ovary	20	Bicornate uterus	1
Uterine pregnancy	11	Gangrenous appendix	1
Hematosalpinx	8	Retained stem pessary	1
Pelvic abscess	7	Missed abortion	1
Large simple cysts of ovary	6	Papillary cyst adenocarcinoma of	
Tubal pregnancy	5	ovary	1
Placental remnants	3	Carcinoma of fundus	1
Placental polyp	3	Accidental tear of bladder	1
Carcinoma of the cervix	2	Accidental perforation of rectum	1
		Thrombophlebitis	1

Simple cysts of the ovaries, slight fibrinous adhesions and unusually large myomas were not included as complications. They occurred in numerous instances but added nothing to the surgical procedure. Ovarian cysts were included only when larger than a fetal head. Intraligamentous myomas were listed only when the layers of the broad ligament had to be separated to expose them. Small nodes pushing out into the broad ligaments were not considered. Patients reported as having pelvic peritonitis are those having dense adhesions of bowel, omentum, and oftentimes bladder. Minor adhesions of adnexa and rectosigmoid because of a gonorrheal salpingitis and pelvic peritonitis were reported as salpingitis or diseased adnexa. The tubal pregnancies, one of which had ruptured, were all undiagnosed but the uterine pregnancies complicated by myomas were diagnosed in four instances and unrecognized in seven.

The incidence of malignancy complicating the myomatous uterus or cervix is not considered here because of the fact that the cases diag-

This clearly demonstrates the increased risk of removing both adnexa with the uterus. Undoubtedly, if the adnexa had not been so badly diseased and adherent to the structures within the pelvis, the mortality would not have been as high as it was. Therefore, pelvic peritonitis greatly adds to the risk of a supravaginal hysterectomy.

In 68 of the fatal cases the myomas were complicated by pelvic inflammatory disease, an incidence of 85 per cent. The remaining complications were a twisted ovarian cyst with a uterine pregnancy, intraligamentous fibromyoma, Meekel's diverticulum, tubo-ovarian abscess and an accidental bladder injury.

A comparison of the mortality for supracervical hysterectomy in other large series is shown in Table VI. This has been taken from Read and Bell with the addition of the series of Samuels and Edlavitch,⁷ Danforth⁶ and Greenhill. Table VII also taken from Read and Bell gives the mortality in large series of supracervical hysterectomies performed for fibromyoma of the uterus.

TABLE VI. MORTALITY FOR SUPRACERVICAL HYSTERECTOMIES FOR VARIOUS INDICATIONS

Read and Bell	1739	2.1%
Greenhill	1408	4.6%
Amreich	1253	1.6%
Fullerton and Faulkner	609	4.4%
Danforth	304	0.28%
Samuels and Edlavitch	303	2.6%
W. Fletcher Shaw	232	3.05%
Masson	217	1.8%
Burch and Burch	166	4.2%
Weibel	—	4.25%

TABLE VII. MORTALITY FOR SUPRACERVICAL HYSTERECTOMIES FOR FIBROIDS

Mayo and Mayo	3085	1.2%
Schmitz	3129	2.1%
Read and Bell	1159	2.0%
Alsobrook	1000	2.7%
Amreich	624	1.4%
Lockyer	284	1.76%
Miles Phillips	258	1.16%

SUMMARY AND CONCLUSIONS

1. The mortality of 2.1 per cent in the series of 3,129 cases compares favorably with that of other large series on similar types of patients.

2. Fibromyomas of the uterus are the most common tumors found in women and necessitate about 72 per cent of all supracervical hysterectomies.

3. Inflammatory disease of the pelvis complicated 38 per cent of this series of fibroid cases and greatly adds to the operative risk and mortality.

4. The most frequent causes of death in this series were generalized peritonitis in 46.2 per cent; shock in 25.6 per cent; hemorrhage in 6.7

MORTALITY

There were 78 deaths, a mortality rate of 2.1 per cent. This is exactly the same death rate as reported by Read and Bell for 1,739 supravaginal operations performed by the staff of the Chelsea Hospital during a ten-year period.

Table IV lists the causes of death in the order of their frequency. In only a few instances were autopsy reports attached to the history. In the remaining cases the cause of death was taken from the follow-up record and checked by the recorded findings. Greenhill⁵ in a study of the deaths following 6,022 gynecologic operations performed at the Cook County Hospital divides the mortality of supravaginal hysterectomy into two groups. In uncomplicated supravaginal hysterectomies it was 0.8 per cent. In supravaginal hysterectomies plus bilateral salpingo-oophorectomy it was 8.9 per cent. The total number of deaths in the fibroid group of his series was 69, of which 51 followed the supravaginal operation. Four occurred after the uterus alone was removed, four after the uterus, both tubes and one ovary were removed and forty-three after the uterus and both tubes and ovaries had been extirpated. In many of the cases in which both adnexa were removed, inflammatory adhesions bound these structures to the uterus and culdesae, adding greatly to the difficulty of performing the operations.

TABLE IV. MORTALITY IN ALL CASES

Generalized peritonitis	36	46.2%	Toxic Goiter	2
Surgical shock	20	25.6%	Injury to bowel and peritonitis	1
Secondary hemorrhage	6	7.7%	Evisceration	1
Pneumonia	4	5.1%	Cardiac failure	1
Embolism	3	3.8%	Meningitis	1
Uremia	2		Ischiorectal abscess	1

The incidence of peritonitis among the deaths in Greenhill's cases was 50.8 per cent, while embolism occurred in 13 per cent. Embolism according to Read and Bell is more likely to follow subtotal hysterectomy for fibroids than for any other operation. It was responsible for 35.1 per cent of the deaths in their series while peritonitis only occurred in 8.1 per cent. In the present series embolism occurred in but 3.8 per cent while peritonitis was responsible for 46.2 per cent. The high incidence of pelvic infection is also responsible for this difference.

The operations performed in the 78 fatal cases are given in Table V.

TABLE V. OPERATIONS FOR THE 78 FATAL CASES

Abdominal supracervical hysterectomy	5
Abdominal supracervical hysterectomy, bilateral salpingo-oophorectomy	71
Abdominal supracervical hysterectomy, bilateral salpingectomy, unilateral oophorectomy	2

SPLENOMEGALY IN PREGNANCY*

WILLIAM B. SERBIN, M.D., CHICAGO, ILL.

(From the Obstetrical Services of Michael Reese and Wesley Memorial Hospitals)

ENLARGEMENT of the spleen as a complication in pregnancy and labor is sufficiently rare to warrant the addition of all observed cases to the literature. Within a period of four months three such cases were observed, two occurring in Banti's disease and one in chronic malaria. Splenic tumor has also been reported in purpura hemorrhagica complicating pregnancy.

Allen (1924) reported two cases of splenic anemia complicating pregnancy. The first patient died suddenly during delivery; the second patient was treated with x-rays and carried to term in her first pregnancy. In her second pregnancy therapeutic abortion and sterilization were done and followed in one month by splenectomy. The spleen weighed 885 gm.; there was no liver involvement and the patient recovered. Birdsall, Hubert and Wheelchel (1925) reported a case of splenic anemia which they called Banti's disease in its terminal stage, in a primipara, aged thirty-three. During pregnancy there was a progressive anemia treated by transfusion. The patient had a spontaneous delivery at term; the baby was stillborn. The spleen and liver were both enlarged and the patient continued to have uterine bleeding. She improved slowly; there is no mention of splenectomy. Hesseltine (1930) reported a case of Banti's disease in a patient aged forty-two who had had progressive enlargement of the abdomen for two years prior to her pregnancy. In the second trimester a splenectomy was done. The patient went to term and delivered spontaneously. Ashton (1934) reported a case of Banti's disease in the puerperium in a para i aged twenty-five. The patient had had a moderate anemia; she had a ten and three-quarter hours' labor at term; forceps delivery followed by postpartum hemorrhage. On the fourth postpartum day she had a palpable spleen and was given a transfusion. Five months after delivery a splenectomy was done followed by blood transfusion. The liver was small, firm, and hobnailed. The patient died on the thirty-third postoperative day following the removal of packing. Larrabee (1934) gives a brief history of a patient aged twenty-five who aborted five months previous to her admission on a medical service. She had an ascites; splenectomy and transfusion were done. The spleen weighed 420 gm.; there were marked fibrosis and cirrhosis of the liver. Smith, Morrison and Sladden (1933) reported a case in a patient aged thirty-one years, three months pregnant. The patient had a splenomegaly with a possible Banti's disease. She suffered a spontaneous rupture of the spleen; splenectomy was done and the patient went to term. McKenzie (1936) recently reported a case in a gravida iii with a large mass in the left upper quadrant; the liver border was 5 cm. below the right costal margin; the uterus was the size of a two months' pregnancy. A diagnosis of splenic anemia with early Banti's disease was made. Splenectomy was done in the third month of pregnancy under spinal anesthesia. A scar in the liver was excised; the spleen weighed 1,100 gm. This patient made an uneventful recovery, went to term and delivered spontaneously. Malaria in pregnancy has been reported by Blacklock and Gordon, Buckingham, Clark, Deromps, Unger, Wickramasuriya and Wislocki.

*Read at a meeting of the Chicago Gynecological Society, November 20, 1936.

per cent; pneumonia in 5.1 per cent and embolism in 3.8 per cent. Embolism occurred less frequently than in similar series reported by various authors.

5. Seventy-one of the 78 fatal cases had supracervical hysterectomy plus total salpingo-oophorectomy. As shown by Greenhill in the same group of cases, such operations are the most serious because the mortality for this operation is about ten times as great as for simple uncomplicated supravaginal hysterectomy.

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DISCUSSION

DR. J. P. GREENHILL.—I do not think there is much value in comparing the results obtained at the Cook County Hospital with those at other hospitals because of the difference in the types of patients operated upon. The chief value of such an analysis as Dr. Schmitz has presented is to the surgeons whose cases were analyzed.

As Dr. Schmitz has shown, there is a vast difference in the results of supracervical hysterectomy and this operation combined with removal of both adnexa. I found this to be true in my series of cases where the greater operation had a mortality eleven times as high as the simple supracervical operation. Because of this, I do not hesitate to leave a portion of inflamed tube or ovary attached to adherent bowel rather than forcibly to separate the badly infected adnexa from the intestines. The risk of damage to the intestines is thus eliminated and in my follow-up of many of these patients I have not seen any harm from leaving portions of adnexal tissue attached to the bowel.

In my series, among the patients who had only a supracervical hysterectomy the death rate was 0.8 per cent, whereas among those who had a supracervical hysterectomy combined with removal of both tubes and ovaries, the mortality was 8.9 per cent, or eleven times as great.

DR. FRED L. ADAIR.—Dr. Schmitz gave a total of 78 fatal cases with simple supracervical hysterectomy and 7 with removal of both adnexa. The mortality figures would be more significant if we knew the number of operations done in each of these two groups.

DR. HAROLD O. JONES.—I would like to ask if Dr. Schmitz intentionally omitted endometriosis as a complication in fibroids for it has been common in our experience.

DR. SCHMITZ (closing).—I did not include endometriosis because that condition is not filed as myoma in the record room at the County Hospital, and it would have been too much labor to have gone through ten years of records.

Although I believe the value of this presentation is mostly for those who are doing the work, I have tried to compare the mortality rate with other large series of cases taken from similar charity institutions. As I said, it compares favorably with those.

was due to Banti's disease. Feb. 25, 1935, Aschheim-Zondek test strongly positive. Mar. 21, 1935, transfusion of 450 c.c. citrated blood. Mar. 23, 1935, splenectomy done under ethylene ether anesthesia. Liver and spleen both enlarged. The patient made a fair recovery and was discharged on the twenty-sixth postoperative day.

Pathologic Report: Spleen weighed 800 gm. and measured 22 by 11.5 by 7 cm. Microscopic: diffuse hyperplasia of endothelial tissue and fibrous tissue; lymphoid follicles increased.

Obstetric History.—On Aug. 8, 1935, patient was readmitted in labor about three weeks before term. Labor was irregular for a period of about four days. August 12, patient delivered spontaneously; O.L.A., stillborn fetus, weight 5 pounds 4 ounces. Ether anesthesia. The patient received infundin and ergot, each 1 c.c.; there was no postpartum hemorrhage. The patient was afebrile for eight days following delivery but on August 19 had a temperature of 101° F. and complained of numbness of the left hand and arm. Later in the day the left facial muscles were paralyzed; this was followed by paralysis of the left arm and left leg. Blood pressure 182/100. Provisional diagnosis, cerebral hemorrhage or embolus. August 20, 50 c.c. of 50 per cent glucose was given intravenously to relieve the cerebral edema. August 24, pain in the left chest; intranasal oxygen was given. August 25, patient had a definite pneumonia, the left upper lobe being entirely consolidated; she was cyanotic and dyspneic. September 1, severe pain in left leg; great toe discolored. It was believed that there was a thrombus in the popliteal artery of the left leg. September 8, patient became extremely cyanotic, the temperature reached 106.2° F., followed by death.

Postmortem.—Anatomic diagnosis: necrotizing endometritis following parturition. Thrombosis of uterine, internal, and common iliac veins and inferior vena cava. Embolism of both rami of pulmonary artery. Mural thrombi of right atrium, auricular appendage, and ventricle. Multiple hemorrhagic infarcts of lungs. Bilateral hypostatic pneumonia and pulmonary edema. Embolism of left common iliac artery and thrombosis of left femoral vein. Edema and gangrene of left lower extremity. Cerebral embolism. Bilateral fibrous pleurisy with complete obliteration of right pleural cavity. Moderate hypertrophy of left ventricle. Healed calcareous tubercle of right upper pulmonary lobe. Spleen absent, fibrous adhesions of the peritoneum and thrombosis of the splenic artery and vein. Liver weighed 1,930 gm.

CASE 2.—L. R., aged twenty-three, gravida ii, white; admitted Oct. 19, 1935, complaining of abdominal pain. In July previous the patient had had a splenectomy in the fourth month of pregnancy. Her last pregnancy (1934) had been terminated by therapeutic abortion because of an enlarged spleen. On her second admission to the hospital, she was six and one-half months pregnant, and because of the severe anemia it was decided to empty the uterus, by the insertion of a bag under ethylene anesthesia (Oct. 29, 1935). After twenty-four hours the bag was removed, the anterior lip of the cervix was incised and the baby delivered by version and extraction. It weighed 3 pounds 12 ounces, and lived about one-half hour. November 17, left leg edematous and painful; thrombophlebitis. November 30, abdominal distress and ascites; December 4, ascites increasing; edema of right leg. December 12, paracentesis, 5,000 c.c. of straw-colored fluid removed from abdomen. December 23, ascites, dyspnea; 3,000 c.c. clear straw-colored fluid removed from abdomen. Jan. 14, 1936, omentum attached to rectus sheath; less distention; patient also given a 500 c.c. blood transfusion. The patient was discharged January 15. She was worse on discharge, and died at home one week later. No autopsy.

Malaria complicating pregnancy is rare in this part of the country.

Banti's disease or splenic anemia has been defined as a primary disease of the spleen of unknown etiology, characterized by enlargement of that organ, anemia, tendency to hemorrhage and secondary cirrhosis of the liver, with jaundice and ascites. The spleen is the primary seat of the disease and in the later stages it is greatly enlarged. The splenic vein and the portal vein are also enlarged. Microscopically, there is marked fibrotic infiltration and Banti described a proliferation of the endothelial cells of the venous sinuses of the pulp, which he thought were characteristic of the disease. The disease is chronic and because of the decreased fragility of the red blood cells together with distended varices, hemorrhage may be a common feature. In addition to nosebleed, hemorrhage from the bowel, and hematuria—in women there may also be metrorrhagia. Jaundice occurs when there is liver involvement. Pregnancy aggravates the disease although the reverse does not seem to be true. Both medical and surgical measures must be instituted if the pregnancy is to be successfully terminated, as well as to improve the patient's general condition. In the nonpregnant state, early splenectomy followed by blood transfusion is the best treatment. The same medical and surgical principles may be

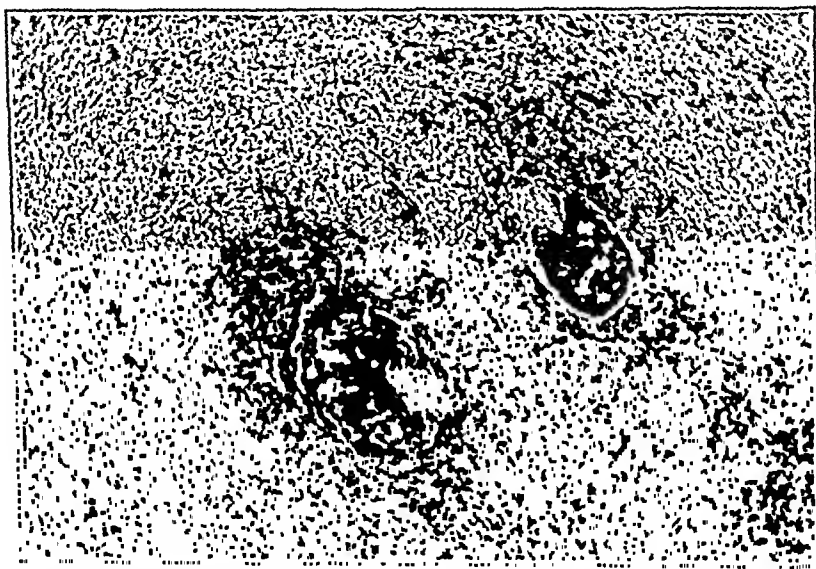


Fig. 1.—Case 1. Section of spleen (low power). Lymphoid follicles sharply demarcated. Marked proliferation of lymphoid elements in adjacent pulp. Sinusoids packed with red blood cells; increase in fibrous connective tissue throughout parenchyma.

followed during pregnancy. Where the disease has become chronic and severely aggravated by pregnancy even radical treatment may fail. Although the cases herewith reported terminated fatally, there seemed to be improvement for a short time following splenectomy, and these cases proved the deleterious effect of pregnancy upon the disease.

CASE 1.—M. W., aged thirty-three, gravida iv, white; admitted Feb. 17, 1935, complaining of an abdominal mass and amenorrhea. There was slight nausea and vomiting which was of recent origin. For the past two years the patient had been in good health. Family history irrelevant; there were three previous pregnancies, the last two of which were terminated by induced abortion, 1931 and 1932. Last period Nov. 22, 1934. Sclera slightly icteric, no lymphadenopathy, mass in abdomen occupying entire left upper quadrant 20 cm. below seventh costal cartilage. Notch felt in spleen, mass in right upper quadrant extending 3 cm. below the costal margin. No ascites. Wassermann negative. Blood pressure 116/70. By careful differential diagnosis, it was decided that the enlargement of the spleen and liver

Chronic malaria with enlargement of the spleen is not usually considered an indication for splenectomy. In our case, the enlarged spleen of 1,200 gm. gave rise to persistent pain as the uterus increased in size. After careful deliberation, it was decided to remove the organ and the patient's convalescence, subsequent pregnancy, and labor were uneventful. However, quinine therapy may be instituted with safety, even in large doses, to prevent malarial intoxication, abortion, stillbirth or transmission of malaria to the fetus. The puerperium is a critical period inasmuch as a recurrence during this period, followed by chills and fever, may be mistaken for puerperal sepsis. Blood smears should be made to differentiate puerperal malaria from puerperal sepsis.

SUMMARY

1. Three cases of splenomegaly during pregnancy are reported, two of Banti's disease and one of chronic malaria.

2. Banti's disease is aggravated by pregnancy. Preliminary transfusion followed by early splenectomy may be safely undertaken in the pregnant as well as in the nonpregnant state.

3. Enlarged spleen in chronic malaria may call for splenectomy because of its size to permit room for uterine growth. Quinine therapy may be instituted for treatment of malaria during pregnancy to prevent abortion, stillbirth, and transmission to the fetus, or its recurrence during pregnancy or the puerperium.

4. Splenic tumor must be differentiated from other abdominal tumors during pregnancy, particularly ovarian tumors and fibroids.

I wish to thank Drs. Saphir, Strasser and Lotspiech for their help in preparing the slides and photographs.

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30 NORTH MICHIGAN AVENUE

EPISACROILIAC LIPOMA*

EMIL RIES, M.D., CHICAGO, ILL.

(From the Gynecologic Department of Post-Graduate Hospital and Medical School)

THE observation of an apparently unique case and the investigation which it caused me to make has led to the establishment of a clinical and pathologic unit which appears to be new and undescribed in medical literature. Its connection with the symptom of backache must make it of great practical importance.

Mrs. N. K., thirty years old, white, American, hotel worker, operated upon for tubal pregnancy in 1917, for left salpingitis, hemorrhoids and fistula-in-ano in 1929, came for examination April 29, 1936, on account of disabling pain in the back extending to the right hip and thigh which woke her up in the morning and lasted all day. It was increased by bending over. She also complained of painful menses with discharge of clots, leucorrhea, headaches, constipation, varicose veins in both legs which were painful at times.

*Reported at a meeting of the Chicago Gynecological Society, October 23, 1936.

CASE 3.—M. B., aged thirty, gravida ii, white, a native of Arkansas. In May, 1933, the patient was treated for malaria with quinine. Since then she had had an increasing tumor of the abdomen. She reported to the dispensary complaining of a mass in the abdomen and amenorrhea. Vaginal examination revealed a uterus the size of a four months' pregnancy, distinct from the tumor which was in the left upper quadrant. The patient entered the hospital on May 10, 1935, with a diagnosis of pregnancy complicated by an enlarged spleen. After much debate it was decided to do a splenectomy because of the increasing size of the abdomen. She was given a blood transfusion followed by splenectomy. She made an uneventful recovery and was discharged on the twelfth postoperative day. The spleen weighed 1,200 gm. Microscopic diagnosis, fibrous splenitis, typical of malaria. On Oct. 24, 1935, patient entered the hospital in labor. She was about three weeks past term. Fetus in O.D.A. position. Labor lasted seven hours; low forceps delivery. The baby weighed 3,655 gm. Puerperium afebrile. Patient was discharged on tenth postpartum day. Mother and baby apparently normal.

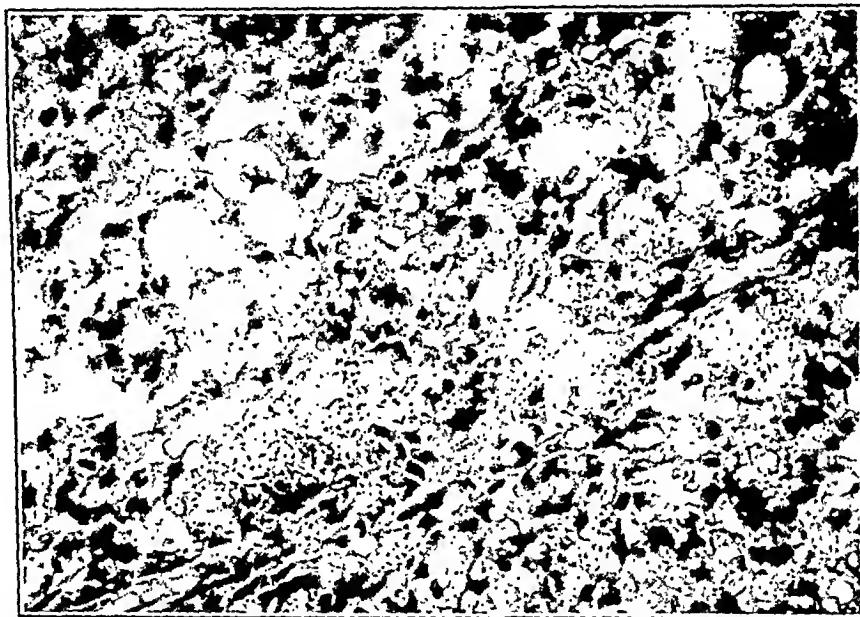


Fig. 2.—Case 3. Section of spleen. Accumulations of fine dustlike pigment within the reticulo-endothelial phagocytes. Sinusoids filled with red blood cells, and increase of fibrous connective tissue.

COMMENT

During normal pregnancy the spleen does not undergo any appreciable hypertrophy. Any enlargement during pregnancy is usually due to preexisting disease, as in the three cases reported here. A moderately enlarged spleen weighing up to 800 gm. may not be disturbing in pregnancy. A spleen weighing 1,000 gm. or over constitutes some embarrassment and is an impediment to a growing uterus. In addition, the pregnancy may be a factor which might aggravate the disease. In cases of Banti's disease, preliminary medical therapy and transfusion followed by splenectomy is good treatment. The latter, when carried out early, may be life-saving. X-ray irradiation over the splenic area has been employed, but its intensive use is not recommended during pregnancy.

In the cases reported here, pregnancy was followed by some improvement after splenectomy; the literature reveals other patients who went to term and had normal labors and normal babies following splenectomy.

exposed. The tips of the examiner's fingers pass over the entire sacral and the neighboring iliac regions. The posterior sacral surface having many irregularities, it is necessary to exclude bony prominences. Therefore, no tumors are counted as positive which cannot be moved freely.

If the tumor is declared sensitive to touch by the patient, the examination is directed to the surrounding territory and brought back to the sensitive area. No tumor is put into the category of "sensitive" unless the patient identifies the area positively on repeated palpation.

Symptomatology.—A great number of persons have backache, but no episacroiliac lipomas (159 out of 1,000 examined). A great number of persons have such tumors, but have neither backache nor sensitiveness or spontaneous pain in them and are perfectly positive on this point (167 out of 1,000 examined).

But it is a most striking experience to hear a patient who has gone through the whole gamut of medical, gynecologic and orthopedic treatments including drugs, serums, vaccines, plaster-casts, diathermy, etc. exclaim emphatically "that is the point" when his episacroiliac lipoma is touched in the examination. Patients with these painful tumors recognize the area as the seat of their pain immediately, and the pain is elicited promptly by handling, pressing, or moving the tumor.

In some patients pressure on the episacroiliac lipoma is not only painful, but causes pain to radiate from the tumor in different directions.

In the majority of persons with episacroiliac lipomas the tumor would never have been suspected unless a systematic search, such as we carried out, had revealed it.

Since we have carried our investigation into several clinics, the physicians connected with them have had no difficulty in finding episacroiliac lipomas on their own patients independently.

The shape of the tumors is cylindroid or round. The cylindroids are practically always placed transversely. The consistency is that of a more or less elastic lipoma, sometimes that of a soft fibroma. The largest size found so far was that of a silver dollar and as thick as the little finger. The smallest has been no larger than about 1 cm. in diameter. The skin is always movable over the tumors, so much so that a spectator at the examination can see the tumor slip under the skin. The character of the pain is mostly described by the patient as an "ache." Backaches are located in many different regions of the back, but those due to the tumors described here are limited in extent to the neighborhood of the sacroiliac joint, though they may radiate slightly.

Location.—The two characteristic dimples in the sacral region are the most favored sites of these growths. Most of those we have found were within 5 cm. of either dimple. The mobility of the tumor is limited, but distinct. We have found only one patient, aged seventy, whose two tumors could be moved across the midline, where ordinarily the skin has bony attachment. This patient had disk-shaped tumors on each side, the circumference of a silver dollar and the thickness of a little finger. She had no pain in the tumors and was under treatment for cystitis.

In most cases the growths are symmetrical and of similar shape on both sides. In a few one side is larger than the other. Fewer persons are positive only on one side. In very rare cases we have found more than two, as high as four and six, arranged symmetrically in vertical rows over the sacroiliac joint. The patient with four had enough backache to handicap her in her work. The one with six tumors had no backache.

Duration.—None of the persons examined (except the three noted below) had any knowledge of their tumors and therefore none could give us information about the length of time they had had them. But if the symptom of severe backache

Examination showed: Weight 172 pounds. Hyperplastic sinusitis, deflected septum, dental pyorrhea, buried infected tonsils. Chest without pathologic findings. Upper abdomen without findings. Corneal, pharyngeal, patellar, pupillary reflexes normal. There was no infection of the urethra or labial glands. A small fibroid was found in the body of the uterus, otherwise the genitalia were normal. Fistula-in-ano well healed. Blood Wassermann and Kahn negative. Urine normal.

Examination of the sacral region showed a 3 by 2 cm. elliptical tender tumor placed transversely over the lower end of the right sacroiliac joint at about the point of the lateral dimple. It was elastic and of the consistency of a fatty tumor. A smaller tumor, also tender, was found over a symmetrical point on the left side. The patient declared these tumors to be the seat of her pain in the back. On repeated examination the patient located her backache consistently at these two points.

May 20, 1936, the tumors were removed through two small incisions with practically no loss of blood. Under the tumors the periosteum of the sacrum was seen and felt bare. A few linen skin sutures and a compression dressing finished the operation. (For microscopic findings see under "pathology.")

The patient reported freedom from pain at once. Absence of pain in this area was reported repeatedly up to October, 1936.

On account of the location of the tumors and their microscopic diagnosis (see "pathology") I designated them as episacroiliac lipomas.

No previous report of this group of tumors has been found in the literature.

With the cooperation of my associate, Dr. Richard Livvendahl, I undertook the examination of 1,000 persons at random in dispensaries, hospitals, and otherwise, in order to find whether similar cases existed and had been overlooked.*

We have examined 250 males and 750 females. Out of the 1,000 persons examined, 309 had backache in the lumbosacral region; 159 of these were without any tumors. But among the 1,000 examined, 317 had tumors similar to the ones reported above, a ratio of 31.7 per cent. Of the 317 with tumors, 46 were males, 271 females, that is: 18.4 per cent of the males examined and 36.1 per cent of the females examined showed tumors. The small proportion of males examined may well cause the apparent difference. Of the 317 with tumors, 223 were white and 94 colored. Of the 317 with tumors, 150 complained of backache, 167 had no backache. In 131 of the 317, the tumors were spontaneously painful, in 186 the tumors were not painful. In 231 of the 317, the tumors were bilateral, in 86 unilateral.

The age distribution of the 317 with tumors is as follows: under ten, 7; to twenty, 13; to thirty, 67; to forty, 102; to fifty, 80; to sixty, 29; above sixty, 19.

Forty pregnant women were examined and showed the following ratios: 22 had tumors, 14 had tumors and no pain, and 4 had episacroiliac lipomas and pain in them.

It was found that fat patients were as often without tumors as thin ones showed positive findings.

I wish to emphasize that not the remotest connection with the "adiposis dolorosa" of Dercum has been uncovered.

Small lipomas in other parts of the body of persons examined partially were found in two cases out of the 1,000, but complete examination of the entire body was not carried out in the entire series.

The examination is carried out with the subject sitting on an examination table bending forward or lying on one or the other side with the sacral region

*Our thanks are due to the staff of Postgraduate Hospital and Medical School, Dr. H. Tumpeer of the Allergic Clinic of Michael Reese Hospital and to the Gynecologic and Obstetric Dispensary of the Medical School of The University of Illinois (Professor Falls) for facilities extended.

Some twenty patients have so far been treated surgically by exsection or injection of novocaine. The time is too short to report on remote results. Some patients have been relieved at once and have remained free from pain and disability. In others pain in near-by areas or in the area injected has returned more or less. In the first case reported here, pain is complained of, but not in the region where the tumor had been located, but higher up and this patient had a fibroid of the uterus, sinusitis, infected tonsils, deflected septum of the nose, pyorrhea, which she had not yet had taken care of. The original site of the tumors was painless and the patient was working (October, 1936).

Pathology.—The episacroiliac tumors are more or less rounded cylindroids. They have a distinct fibrous capsule and are perfectly smooth on the surface. The cut section shows fat tissue.

Microscopically they consist of fat tissue with very little connective tissue between the fat cells, while the capsule consisted of a little more dense fibrous tissue.

In one case, microscopically a small nerve has been found running through the middle of the tumor (Fig. 1).

The relation of the lipomas described here to neurolipomas is still under investigation.

Conclusion.—A previously undescribed clinical group of lipomas in a special location over the sacroiliac joints is established, to which the name "episacroiliac lipoma" may properly be applied.

The connection of this group of tumors with backaches, their surgical treatment and its results deserve wider attention.

Investigation of the relation to neurolipoma requires more extensive material.

2400 DEARBORN STREET.

ANGIOMATOSIS RETINAE (VON HIPPEL'S DISEASE, LINDAU'S DISEASE) COMPLICATED BY PREGNANCY*

MERVYN V. ARMSTRONG, M.D., F.A.C.S., BROOKLYN, N. Y.

(From the Department of Obstetrics and Gynecology, Long Island College Hospital)

THIS case seems worthy of record, because of the extreme rarity of the condition. It is the second case recorded in the literature, in which pregnancy was noted as a complication and is the first for which cesarean section was performed, with angiomatosis retinae as the sole indication.

Angiomatosis retinae is a disease characterized by immense dilatation and tortuosity of retinal vessels and the development of angiomas usually toward the peripheral retina (von Hippel's disease). It is frequently associated with angiomatous cysts of the brain and spinal cord, and malformations or cysts of various somatic organs. When this association is present, the condition is known as Lindau's disease.

Mrs. M. B., twenty-two years of age, was admitted to the prenatal clinic of the Long Island College Hospital, Jan. 4, 1936, complaining of disturbance of vision and amenorrhea of five and a half months' duration. The medical and surgical history was essentially negative. Menstruation began at thirteen, recurred regularly every twenty-eight days, of four to five days' duration and not painful. This was her first pregnancy. The last period occurred on July 7, 1935, and quickening was noted on Dec. 15, 1935. The estimated date of confinement was April 14, 1936.

The visual disturbance dates from 1930, when the patient was sixteen years old, and attending high school. During routine physical examination in school,

*Presented at a meeting of the Brooklyn Gynecological Society, December 4, 1936.

which was referred to the episacroiliac tumors can be taken as guide, these patients at least had suffered from them for years.

Dr. Lifvendahl has found three patients who knew of their tumors:

A woman, forty-six years old, under gynecologic treatment for two years without improvement, pointed out a tumor over the sacrum. Two episacroiliac lipomas were found on examination, one was removed and one injected with novocaine. Backache was reported absent two weeks later.

A woman, twenty-eight years old, with backache for two months, knew she had tumors over the sacrum. Two were found.

A woman of seventy-two years knew she had a "knot" over the right side of the sacrum for five years and pain in the right side of her back for five years. Two episacroiliac lipomas were found, the right one painful to the touch. The left one was larger, but only slightly tender. No treatment was given.

Treatment and Results.—The treatment of the episacroiliac lipomas has been by injection or by excision.



Fig. 1.—Episacroiliac lipoma. *F*, fat cells. *N*, nerve. *V*, blood vessel.

Injection of 2 per cent novocaine with or without adrenalin into the tumor or around and under it has been a simple way of relieving the pain. The relief has been strikingly rapid, especially in cases of long standing and which have had many kinds of other treatments. It has happened repeatedly that patients who moved bent over and with great distress, straightened out immediately and declared themselves comfortable after the injection. This change would not be deserving of attention, if it were of no longer duration than the usual effect of the injection of a local anesthetic. But the result in a number of cases has endured now for weeks.

In the case of rather large tumors or where injection of novocaine has relieved only temporarily, the tumor or tumors have been excised, usually under local anesthesia. It has always been a simple matter to peel out the tumor from the surrounding tissue and there is very little bleeding. The fact that the tumor shells out deserves emphasis.

SUMMARY

1. A case of angiomas retinae (von Hippel's disease) has been presented.
2. A careful survey of the literature shows that this is the second case of this disease complicated by pregnancy.
3. This is the first case on record, in which angiomas retinae has been accepted as an indication for cesarean section.
4. While up to the present time, there is no definite evidence of an associated Lindau's syndrome in this patient, cases of this type should be followed by both x-ray and physical examination for evidence of pathology in the central nervous system or somatic organs.

The author is deeply indebted to Drs. John N. Evans and Ralph I. Lloyd for their assistance and suggestions in the preparation of this case report.

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85 PIERREPONT STREET

DISCUSSION

DR. HAROLD F. SCHILBACK.—The story of this patient is typical. These cases come to us because there is an insidious loss of vision. The first objective finding is a dilatation of one vein. Shortly afterward there is a dilatation of the artery which accompanies that vein. Usually, the dilatation is particularly noted in two vessels and these may be, as in this case, in the upper temporal area. Shortly following the dilatation we, of course, get exudate both in the retina and beneath it. Later, hemorrhages occur. With the resolution of the exudate, one finds most frequently detachment of the retina because of a retinitis proliferans. As has been said, this patient undoubtedly will go on to complete blindness, because the right eye, with the retinal detachment, is now very much involved.

Frequently a complication arises in these cases whereby there is, on some physical effort, a spontaneous hemorrhage. With that there is, of course, an acute glaucoma. The vessels are extremely large, bleeding is great, and there is very little that can be done about it. You cannot operate for the relief of the glaucoma because that is followed by more bleeding. The patient is in severe pain and the loss of vision is prompt. To avoid such an accident the procedure which has been noted was undertaken.

vision in her left eye was found to be poor. She went to an optometrist, who was unable to benefit her with glasses. She then was referred to the Brooklyn Eye and Ear Hospital, where a diagnosis of angiomatosis retinae was made.

Therapy consisted of intravenous salvarsan, tuberculin, calcium gluconate and x-ray treatment to the head. During the past six years there have been frequent physical and special neurologic examinations, including Barony equilibrium tests and x-ray examination of head and abdominal organs. In less than one year after the onset of visual disturbance in the left eye, the vision in the right eye began to diminish. Vision has become markedly impaired to date, so that at present, the patient can only distinguish between light and darkness. Her eyegrounds have been examined, not only by practically all the members of the staff of the Brooklyn Eye and Ear Hospital, but she was also demonstrated before the New York Ophthalmological Society, The Eye Section of the American College of Surgeons, and the Eye Section of the New York Academy of Medicine.

The patient was admitted to the obstetric ward of the Long Island College Hospital on April 1, 1936, at which time her general physical examination was essentially negative. The pelvic measurements were normal. The uterus was enlarged to size of full-term pregnancy and the fetus was lying in L. O. A. The fetal heart was 140 and regular. Pelvic examination was omitted because cesarean section was being considered. Her blood pressure was 110/60 and the urine, blood count, chemistry, and Wassermann were negative.

The ophthalmologic findings by Dr. Evans on April 3, 1936, were as follows:

Left eye showed secondary cataract, with synechia from a quiescent iris, binding the border of the pupil to the capsule of the lens. The episcleral vessels were slightly congested. The cornea was clear; the anterior chamber shallow. Tension normal.

Right eye showed external structures without evident pathologic changes, nor was there any pathology in the anterior chamber, iris, or lens. A few small vitreous opacities could be seen floating about with movements of the eye. The optic disc was elevated about one diopter, was pink in color and had blurred edges. Emerging from its center were a number of tremendously dilated and tortuous blood vessels. These were most noteworthy passing temporally, where toward the midperiphery, two of them merged in a large, elevated, round mass which was apparently made up of a medusa-like collection of small blood vessels. About these vessels was a translucent zone, which was suggestive of a cyst wall and the adjacent retina was apparently distended and thickened, by the formation of innumerable minute cysts, which suggested the appearance of soapy foam.

As the greatly distended and thickened vessels leave the nerve head, they are accompanied by wide bands of yellowish "snow-bank" exudate. The two greatly dilated vessels extending from the nerve head and running upward and forward toward the nasal periphery were partly obscured by a fold of detached retina, and though their terminations could not be seen, they doubtless ended in a second angioma. Throughout the eyeground occasional small hemorrhages and scattered spots of old and new exudate were noted. The tension was 23 mm. of mercury (McLean). Visual acuity was 10/200.

As a result of this ophthalmologic consultation with Dr. John N. Evans, cesarean section under local anesthesia was deemed advisable. Dr. Evans felt that the already dilated and diseased vessels might not withstand the marked vascular strain, that inevitably accompanies spontaneous labor. The fact that there might be an associated lesion elsewhere in the central nervous system, or in one of the parenchymatous organs also was considered.

On April 9, 1936, a classical section was performed under local anesthesia and the patient was delivered of a normal living male infant weighing 2,940 gm. Sterilization was recommended, but consent was refused by her husband. The postoperative course was uneventful and the patient was discharged from the hospital on April 26, 1936, seventeen days after operation.

DR. ALFRED C. BECK.—I am interested in knowing how the spermatozoa entered the tube. Do you think that they entered from the side of the ectopic or did they cross in the abdomen from the opposite tube?

DR. WILLIAM F. NELMS.—We have been using this method of sterilization at the Brooklyn Hospital for the last fifteen years. We have done 219 cases and have had no reported cases of pregnancy. Dr. Lull, of Philadelphia, tried it out on 223 cases and states he has had no failures reported from a 72 per cent follow-up.

We believe that one of the reasons why this method has been satisfactory in our hands is that we do not produce too much trauma. If too much trauma is produced to the tube either by crushing or the use of nonabsorbable sutures, necrosis results, and it is much more likely to break down and form a fistula.

There are one or two other points in the technic that we use which might be referred to. We do not make so large a loop that when it is ligated too much tension is exerted on the tube. With a large loop the ligature is liable to slip off or cut through the stump. The same thing applies when the loop is made too close to the uterus. Especially in conjunction with cesarean section where there is a large pregnant uterus, if the loop is made near the uterus, and not in the middle portion of the tube, the weight of the uterus moving from one side to another and in involuting, is likely to cause the ligature to cut through.

We have had but one complication in our 219 cases and that was a case of intestinal obstruction that developed about three weeks after the operation. On opening the abdomen in that case we found a loop of bowel adherent to the cut ends of the tube, and on freeing the adhesions around it, there was an escape of one or two drops of pus.

DR. WILLIAM SIDNEY SMITH.—In answer to Dr. Welton, I would like to say that Dr. Pomeroy never used black silk as a ligature in his method of sterilization. He avoided a nonabsorbable suture for the reason that it is liable to leave a fistula. He always used either plain catgut or No. 1 chromic catgut.

DR. LUTZ (closing).—Dr. Beck has asked how the spermatozoon reached the ovum to fertilize it. The right tube had a definite separation midway between its proximal and distal portions where part of it had been resected during attempted Pomeroy sterilization. The cut end of the fimbrie segment of the tube was apparently closed by an adhesion. Therefore, I believe the spermatozoon must have traveled through the uterine portion of the severed right tube, reached the abdominal cavity and found its way to the ovum and fertilized it near or at the fimbrie portion of the tube.

Mayer, A.: *Percutaneous Puncture for Hydramnios During Pregnancy*, *Monatsschr. f. Geburtsh. u. Gynäk.* 104: 259, 1937.

During the last 10 to 12 years, Mayer has punctured the amniotic sac through the abdomen in 12 cases of hydramnios. The indications were pressure symptoms including dyspnea. The technique is simple and the amount of fluid removed varied between 850 and 3,750 c.c. The immediate result was always good because the pressure symptoms subsided immediately. To prevent labor pains morphine and pantopon were given after the puncture. In five cases, however, labor followed in 1, 3, 6, 8, and 10 days respectively. There were no untoward effects encountered, although one patient fainted and vomited. No babies were injured. To avoid the placenta, punctures should not be employed in cases of placenta previa.

J. P. GREENHILL.

ECTOPIC GESTATION FOLLOWING POMEROY STERILIZATION*

MARTIN H. LUTZ, A.B., M.D., BROOKLYN, N. Y.

THIS case is one of a pregnancy, extrauterine, following attempted sterilization by the Pomeroy method.

Mrs. V., a thirty-one-year-old multigravida, was operated upon by me at the Peck Memorial Hospital, Brooklyn, March 12, 1935. The preoperative diagnosis was eight weeks' gestation, complicated by early malignant hypertension, established by her past history as well as the physical findings.

Operation, March, 1935, abdominal hysterotomy and bilateral tubal resection (Pomeroy method). At the time no gross tubal or peritubal pathology was noted. The fallopian tubes were grasped by Allis clamps at approximately their midpoints and a liberal portion, about 4 cm., of the mid-section of each tube was removed. The base of the tubal loop produced by traction on the Allis clamps was ligated as usual by a chromic No. 1 ligature. The patient's postoperative course was uncomplicated, her abdominal wound healed by primary union. Histologic examination of the structures showed no abnormalities.

Approximately one and one-half years later, September, 1936, this patient was reoperated upon by me at the Peck Memorial Hospital. At this time the preoperative diagnosis was right ectopic gestation. The pelvic findings at the time of this operation were as follows: The distal portion of the right tube was the site of a "tubal abortion," so-called. There was moderate hemorrhage into the abdomen. The portion of the right tube involved in the gestation and the right ovary were removed. The proximal or uterine portion of the right tube was resected. Inspection of the left tube showed a separation in its mid-section and adhesions to the sigmoid. Future pregnancy did not seem possible by way of the left tube. Operation was limited to removal of the distal portion of the right tube and the right ovary. Histologic examination of the tubal tissue confirmed the diagnosis of extrauterine gestation. The patient's postoperative recovery was uneventful.

47 PLAZA STREET

DISCUSSION

DR. GEORGE H. DAVIS.—At the Methodist Episcopal Hospital we have had two failures following the Pomeroy sterilization. However, in deference to the method, I must state that in both of those cases, the tubes were tied off with chromic catgut, rather than with plain catgut, as used at the Brooklyn Hospital.

Lately we have been burying the proximal stump of the tube and thus far we have not had any reported subsequent pregnancies. The ease with which this is done depends on how close you tie the tube to the uterus. The stump can be buried very easily, either by a purse-string suture, or between the layers of the broad ligament. It takes only a few additional seconds for each tube, and I do not believe any recurrences will follow.

DR. THURSTON S. WELTON.—I know that Dr. Pomeroy used plain catgut sutures, but I believe that either black or white silk is more satisfactory.

*Read (by invitation) at a meeting of the Brooklyn Gynecological Society, December 4, 1936.

forms of feeble-mindedness, schizophrenia, manie-depressive psychosis, epilepsy, and Huntington's chorea in the mental group; and deafness, blindness and severe hereditary bodily malformation in the physical group of diseases.

On the basis of a vast amount of case material gathered in Germany and elsewhere, Ruedin's prognostication of the probable recurrence of disease is illustrated in the following few samples. In the case of one parent affected by hereditary feeble-mindedness, at least one child in three may be feeble-minded, and only an exceptional issue will not be feeble-minded if both parents are thus affected. Likewise he believed that 9 to 10 per cent of the issue of one schizophrenic parent may be schizophrenic, while 17 per cent will be the schizoid type of individual and 22 per cent may be affected by other types of abnormality. At least one-half of the offspring inherit the disease if both parents are schizophrenic and in addition nearly one-third of their issue will be schizoid individuals. In manie-depressive psychosis the incidence of recurrent disease when one parent is affected will be about one child in three and an additional one in six will be a cycloid psychopath and nearly one in eight will be affected by other types of abnormality. Studies from Sweden show that two out of five offspring of deaf-mutes inherit the disease from their parents.

Studies of this kind exemplify the type of factual data which underlie the recent sterilization legislation in Germany. Medical opinion here and abroad is divided on the validity of some of the assertions of Ruedin and his followers. Final judgment must await the gathering and presentation of factual data on a scale which will permit definitive conclusions.

The foregoing figures show clearly that the problem of the hereditary transmission of disease is a formidable one, which offers large scope for medical science. The proportion of individuals who, because of hereditary conditions, are unable through their own efforts to provide for themselves and their offspring is conservatively estimated at 3 per cent in any population. Such proportions reflect the continued inbreeding of persons afflicted with hereditary diseases and are accentuated by the emigration of more competent elements in the population to more favorable areas.

The proponents of European sterilization argue that propagation of the unfit can be prevented by no means other than sterilization, for this is the only reasonable and humane way to limit offspring without requiring the intelligent and voluntary cooperation of the parents. Intelligent voluntary cooperation, they say, is not to be expected of the great majority of persons thus afflicted. They also point out that the public is gradually coming to demand that physicians sterilize individuals for a variety of reasons which are not wholly medical. Under the criminal laws in most European countries, sterilization would be considered a mutilation of the body despite its having been performed at the patient's request. It has, in fact, recently resulted in the prosecution of physicians in Graz, Austria; in Offenbach, Germany, and in Bordeaux, France. It is held that the physician is entitled to legal protection. Those who favor sterilization point out that funds are required for the hospitalization of those suffering from severe hereditary diseases, and for the maintenance of their families. These are social costs upon the commonwealth, and are of sufficient magnitude to warrant an interest

Symposium on Sterilization

EUGENIC STERILIZATION LAWS IN EUROPE*

MARIE E. KOPP, PH.D., LARCHMONT, N. Y.

STERILIZATION is a recent addition to the armamentarium of preventive medicine, and it is the United States which has pioneered in the development of eugenic sterilization for those unfit for procreation by virtue of severe hereditary afflictions, as the first statute in the world was enacted in the State of Indiana in 1907. There are now 28 states in the Union with a similar provision written into the statutes. America therefore served as example to the rest of the world.

Closer attention to the background of European laws, the oldest of which is but seven years old, reveals that sterilization was advised on eugenic and therapeutic grounds as far back as 1892 by Dr. August Forel in Zurich, Switzerland. Forel initiated the 1901 *Swiss Law for the Protection of the Insane and Feeble-minded* which authorized physicians to employ whatever therapy they deemed necessary to improve a patient's condition.

In Germany, there were sterilization bills before the Prussian Legislature in 1903, before the Saxon Legislature in 1923, and before the Reichstag in 1907 and 1925. In addition, most of the preliminary work was completed for the enactment of the present sterilization law before the political upheaval occurred early in 1933. The first European law was passed in 1928 in the Swiss Canton de Vaud, and was followed in quick succession by Denmark in 1929, Germany in 1933, Sweden and Norway in 1934, in Finland and Danzig in 1935 and in Estonia in 1936. The Swiss enactment was particularly noteworthy in view of the well-known Swiss opposition to legislative regulation.

In ten other countries sterilization on eugenic grounds has been or is being discussed before the legislatures, and enactment is expected in the near future.

The sponsorship of eugenic sterilization legislation in Europe emanated from each medical group, as the psychiatrists, obstetricians, public health officials, and from the social welfare boards.

The German law is based on thirty years of research in psychiatric genealogy under the leadership of Dr. Ernst Rüdin. The German Psychiatric Research Institute in Munich has undertaken extensive studies of the incidence of diseases believed to be hereditary in origin. A most fertile field for study has been the northern slopes in the Alpine region, Switzerland, Bavaria and western Austria, a well-known goiter area. It is on the basis of such investigations that the German Legislation specified the hereditary condition serving as indication for eugenic sterilization under the 1933 Law. These are the hereditary

*Read before the Section on Obstetrics and Gynecology, New York Academy of Medicine, November 24, 1936.

extreme sexual delinquents or persons of marked sexual abnormality, but this is a therapeutic measure which is utilized as a last resort when all others have failed.

Sterilization for therapeutic reasons on strictly medical grounds is left to the judgment and discretion of the attending physician. Only the German law provides that sterilization carried out for therapeutic reasons must be recorded at the District Public Health Office, as a safeguard in case of later manifestation of the hereditary disease against future action on the part of the state under the sterilization law.

Sterilization for the sake of convenience, that is, for humanitarian social and economic reasons, is legally recognized in some countries, while others characterize such an operation as a criminal offense on the part of both physician and patient. Where the law permits, therefore, the physician is free to grant a patient's request for sterilization on almost any reasonable ground.

The European machinery for sterilization has been planned to minimize the abuses of the legal right to perform the operation. The written application for sterilization may be made by the individual who desires sterilization, or by a guardian on behalf of a minor or an incompetent. Under the latter designation are included superintendents of public institutions for the feeble-minded, the insane, and the criminal. In the Scandinavian countries and in Switzerland members of the petitioner's family may file the application, whereas under the German law this is not possible except in the case of a member of the family who has been appointed as legal guardian of a minor or an incompetent. This prohibition also extends to representatives of the state, e.g., the district attorney, the mayor, or any other representative of the domiciliary or municipal government.

Without exception the European laws stress the point that the applicant for sterilization on his own behalf, or on behalf of another person, must be thoroughly familiar with the character, purpose, and effects of the operation. The laws then require that the local medical officer make a careful study and report on the health of the petitioner, his mental development and hereditary background, the nature and course of the disease, the environmental circumstances and other contributing factors.

The European laws enacted to date emphasize the voluntary spirit with which it is desirable to have the petitioner make his application, submit to careful investigation, and follow out the decision made in his case.

However, the German law provides for the compulsory sterilization of those hereditary defectives who are unwilling or unable to seek sterilization, unless they choose segregation in state-supervised institutions. The law in each other country is compulsory only with respect to public charges who do not need permanent institutionalization on other grounds. A public charge as defined under the European civil laws is an individual whose partial or entire maintenance is defrayed from funds of the commonwealth of domicile or from that in which he holds rightful citizenship. Under the provisions of the Social Welfare Acts on the continent of Europe, collateral relatives can be held responsible for the cost of maintenance of a kin in the ascending or descending line, as well as for blood kin of first and second degree.

in their reduction. Without expensive segregation, the unsterilized mental defective easily falls prey to unscrupulous individuals. There is, finally, the basic eugenic argument used by adherents of sterilization, that the quality of the population is subject to deterioration if the propagation of the hereditarily unfit is allowed to continue unchecked.

Such views have been sufficiently prevalent in Germany and in the Scandinavian countries to force the passage of sterilization legislation. Measures to "render a person unable to propagate" are to be undertaken in the interest of the "public good," in the wording of several of the laws. Hence, most of the laws are aimed at those hereditary diseases which seriously interfere with ability to provide for subsistence and to make the expected adjustments of modern life. In some countries the issuance of marriage licenses to epileptics, deaf-mutes and adult feeble-minded, with a mental age of nine or less, is made conditional upon their previous sterilization. The German law limits the indications for sterilization to those specific disorders in which they believe that transmissions to offspring will result, except that it also includes habitual drunkenness. The latter is defined as a state of such persistent and severe alcoholism that the patient requires repeated institutionalization or imprisonment for his behavior while under the influence of alcohol. The severe physical malformations mentioned in the German legislation are those which seriously interfere with locomotion and those which are grossly offensive.

Some laws specify that only the individual with an "incurable" hereditary disorder, and whose progeny would in all probability be similarly afflicted, may be sterilized, while others assert that the "preventable" and not the "incurable" quality of a hereditary disease makes sterilization desirable. The proponents of sterilization argue that the most extreme cases of mental disease require institutionalization in any event, whether from the point of view of the individual or of the community, and hence do not need sterilization. In some countries only the individual technically a public charge comes under the provisions of the law. In others the outward manifestation of a hereditary disease and the ability to procreate determine the issue. In a third group, carriers of diseased genes in badly affected families, and persons affected with noninheritable diseases, can avail themselves of the provisions of the law.

While taking full account of the hereditary aspects of mental and physical diseases and abnormalities, the sterilization laws do not, as a rule, cover persons suffering from infectious diseases, or such asocial individuals as criminals and habitual paupers. Nor do they apply to those individuals whose mental and physical condition prevent their returning to life in the community and necessitate continued segregation. The sterilization of institutionalized individuals would be an unnecessary strain and expense, unless institutionalization failed to prevent procreation. In Germany the individual adjudicated unfit for procreation, who for religious and other reasons objects to sterilization, has the alternative of segregation for the period of his reproductive life and in a state-supervised institution. The age of puberty determines in most countries the lower age limit, while the upper age limit for women ranges from thirty-eight to forty-five and for men from sixty on.

The social-eugenic laws in Norway and Finland, and the criminal laws in Germany and Denmark contain legal provisions for the castration of

of the operation resemble those of physiologic sterility from disease or other causes. It is, therefore, believed that mental and physical disturbances are highly unlikely sequelae of sterilization, as it is being performed under the law.

The costs entailed by the sterilization proceedings, the operation and the hospitalization, are borne by the institution normally charged with the care of the defective individual. In Germany, all legal proceedings are the financial responsibility of the State; the charges for operation and hospitalization are paid by the individual, the sickness insurance fund, or by the Board of Public Welfare. The sickness insurance covers a minimum amount above which the individual is responsible. The cost of institutionalization in Germany of those individuals who object to sterilization on religious or other grounds must be paid by the individual, his family, or by friends, and is never paid by the State.

Reports on the application of the Danish law show that 127 individuals have been sterilized since 1929. In the Canton de Vaud, Switzerland, 48 operations were performed during ten years before the enactment of the law in 1928; from that date until January, 1935, 46 additional operations were performed. In other Swiss urban centers, where there is no restrictive legislation, such operations are more frequent. In Germany, since the law went into effect on Jan. 1, 1934, the 205 Hereditary Health Courts have adjudicated more than 200,000 candidates for sterilization. The vast difference in these figures, even on a per thousand of population basis, measures some of the difference among the various laws as regards the scope of their compulsory features.

Experience with sterilization has been altogether too limited to furnish a factual basis for discussing the relative merits of voluntary and compulsory sterilization.

Increasing urbanization and mobility of the people, resulting in the location of families in new surroundings where they are not known by their neighbors or by the authorities, present a serious problem. This is the fundamental reason for the much discussed and often resented legislative regulations of many personal matters.

Here I may add that sterilization of those deemed unfit for procreation because of hereditarily conditioned defects is only one part of a program to improve the competence and health of the people. The European legislation movement to make the issuance of a marriage license conditional upon prenuptial medical certification will be, it is believed, the most effective single educational measure to improve the health standards of the people.

In charge of the investigation in each country is the Department of Public Health which is responsible for filing petitions for sterilization proceedings. The individual decisions are made in the name of the commonwealth after independent referees and special witnesses have been heard. Thus the operating surgeon or gynecologist is relieved of the responsibility of decision under the eugenic provisions of the law.

In the Scandinavian countries and in Switzerland the authority for such decisions rests with the Departments of Public Health and Social Welfare, while in Germany it is in the hands of the specially constituted Hereditary Health Courts. Actual decisions are usually made by small boards, committees, or courts with four to six members: a lawyer familiar with the routine of the Family or Domestic Relations Courts; a psychiatrist; a physician trained in medical genetics; and one or more physicians from general practice or engaged in various specialties.

The German law provides that no medical, legal, or governmental official may serve on more than one body rendering decision on a given case. This stipulation has been drawn to prevent conspiracy against an individual. The sterilization proceedings and hearings are not public, and all relevant data are held confidential, since medical, legal, and governmental witnesses are obliged to divulge information without constraint. Failure to maintain secrecy is punishable by fine or imprisonment. Most of the European laws provide for appeals from the decisions made by the responsible authorities.

Sterilization operations must be performed in hospitals approved by the Department of Public Health. Such hospitals must not only be equipped with adequate facilities for operation, but must also be prepared to care for mental cases during the period of convalescence. Only surgeons and gynecologists licensed to practice as "specialists" in their fields are allowed to operate.

The sterilization laws customarily require that the operation follow the decision as soon as possible. The German legislation specifies that no person may be subjected to sterilization if the operation would endanger his life. It is partly for this reason that all admissions for sterilization are given thorough medical examinations and diagnostic laboratory tests. If the surgeon in charge of the hospital believes sterilization to be inadvisable because of previously undiscovered disease, or because the success of the operation might be jeopardized, the law permits a postponement of the operation.

The operative technique is determined by the surgeon, who is thus free to use the method most familiar to him. The law specifically states that the method of sterilization shall be operative, except that irradiation is upon special indication permitted for women over thirty-eight years of age. Legally, the operation is understood to be a severing, tying or occlusion of the vas deferens, or of the fallopian tubes, but not a removal or mutilation of any other parts of the reproductive system. The operation must not interfere with endocrine balance or with sex desire or response. In all European countries a written report on the method of operation, the course of convalescence, and on the subsequent mental and physical state of the patient must be filed by the surgeon with the Public Health Office.

In European medical and psychiatric circles it is argued that, with operative procedures conservatively limited to the severing, tying, or occlusion of the vas deferens or of the fallopian tubes, the after-effects

who loops the tube in its middle portion, ligates with silk sutures and cuts off the loop; of Peitman, who ligates the tube with silk in two places about 2 cm. apart, splits the peritoneum exposing the tube, excises a section of the tube between the ligatures and then sews the split peritoneum over this with fine silk sutures. He calls this, "subserous partial tubal extirpation"; of Rabinowitz, who does just a Peitman, except that he sews the ends of the cut tubes with silk and buries the uterine stump in the musculature of the uterus; of Planner, who ligates doubly with silk, cuts between the ligatures, sews the ends with silk and buries the uterine stump in the broad ligament; of Hofbauer, who cuts the tube, ligates the proximal end with silk and approximates the round and ovarian ligaments over the stump; of Madlener, who loops the tube, crushes it together with mesosalpinx and ligates the silk or catgut sutures; of Williams, whose routine method is to excise the proximal end of the tube from the uterine horn by a wedge-shaped incision, carefully closing the wound with fine sutures.

The late Dr. Hussey of Brooklyn had an ingenious and fairly simple method of ligating and cutting the tube. With the end of the ligature, he pulled the distal portion down between the leaves of the mesosalpinx in a reversing direction, then whipped this slit over with the same suture which was carried over to close the opening in the uterine horn. I did this a number of times but occasionally general venous ooze necessitated a salpingectomy.

If sterilization is to be done at the time of an early pregnancy, instead of hysterotomy and tubal resection hysterectomy has been advocated. It is somewhat more serious surgery and also the resultant lack of menstruation may unnecessarily produce mental depression. In the tuberculous, it is more to be considered, for among the workers in that field there is definite feeling that each menses brings on or adds to fever and patients do not do as well.

With all these in mind, Pomeroy sought for a simpler procedure and produced a modification of Madlener's method. Madlener crushed the base of a loop of tube and ligated with a silk suture. Pomeroy caught up a loop of tube in its most flaccid portion, ligated the base with absorbable suture and cut off the loop. His theory of this sterilization was that the peritoneal exudate thrown out would, after absorption of the catgut, make a serous barrier over each cut end. Its simplicity is perfectly obvious, and its safety lies in the factor of its short-time consumption and more particularly its lack of hemorrhage risk. In this audience of expert pelvic surgeons those two factors may be dismissed for discussion.

As to the *surety* of this operation, like all others, there has been debate. In our original report in 1929 no pregnancies had followed the procedure as done at the Brooklyn Hospital or the Methodist Hospital. To get experimental confirmation of our clinical results we used cats and guinea pigs under observation over several periods of "heat" and obtained no pregnancies. On opening the abdomen we found the same results that we did in human beings, a specimen of which I have tonight. Between the cut tubal ends there is nothing but a fibrous peritoneal band.

Lull of Philadelphia in 1935 made the most comprehensive review of results of this method. He condemned all others but had an open mind as to a better method if it could be found. He criticized the others

OPERATIVE METHODS OF STERILIZATION IN THE FEMALE*

ELIOT BISHOP, M.D., BROOKLYN, N. Y.

(From the Obstetric Service of the Brooklyn Hospital)

ASIDE from the indications, which I will not discuss, the subject of sterilization continues to be a moot point. Methods have been attempted since 1850, and I will refer you to the well-known works on sterilization and contraception for the history of this matter. However, in Eastman's article published in the autumn number of the *Journal of Contraception* and in Hyams' address before the American Association of Obstetricians and Gynecologists and Abdominal Surgeons two years ago and in a paper by W. F. Nelms and myself published some six or seven years ago, the best-known procedures are referred to.

One ideal of any method should be for a temporary period, as a time may occur in the life of many a woman who has been sterilized when she wishes, and justifiably, that what has been done could be undone. Twenty years ago Cary did some experimental work on a metal band of resilient consistency that could be snapped around a tube like the trouser clip for a bicyclist. He never carried this idea through any practical experiment however.

In the last few years, Sovak, on Holden's service at Bellevue Hospital, has done well with reconstructing the oviducts damaged by disease. Whether or not they have attempted any after elective sterilization, I do not know.

In most instances, however, sterilization is needed for permanence, so we will confine our discussion to the means of permanently preventing conception without resort to contraceptives. Another ideal is a procedure that can be carried out with no invalidism. Dickinson and Hyams each have attacked this problem with ingenuity. I have seen no figures of follow-up to tell what their results may be. Time, in addition to a large series of cases, is necessary for more than presumption as to its surety. Hyams needs a definite amount of apparatus that is not universally at hand. The amazing ability of a hollow muscular tube to regenerate itself makes one suspicious of the scar in the uterine horn. For reason of its safety, we hope that a reasonably long follow-up will prove the efficiency of this method. In many instances, the need for sterilization crystallizes itself when the abdomen is opened, or about to be, and at that time the abdominal attack is justified.

An elaborate procedure on a tube may develop annoying ooze of blood, especially in the presence of a pregnancy. It may also disturb the blood supply of the ovary with the possibility of cystic degeneration or cystoma formation.

There have been many attempts to destroy continuity of the fallopian tubes; resection and burying the stump, etc., have been done after several different methods, many taking time and open to the objection of producing bleeding. The most commonly used methods are: of Kohler,

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Two methods were used by the early workers, one in which the x-rays were applied to one pelvic area which required treatment over a few weeks or several months and the other administering a massive x-ray dose at once. In 1920 Seitz and Wintz⁵ established their ovarian dose, i.e., that dose of x-ray given through the pelvis which would suppress the menstrual function. The x-rays were administered in one dose through the pelvis directly over the ovarian areas.

Morton,⁴ in the United States in 1903, was the first to report on x-ray treatment of fibroid uterus. Originally it was believed that irradiation effect on fibroids was due only to its suppressed ovarian function; today, however, we know that irradiation produces sterilization because it acts directly on the uterus in addition to its effect on the ovaries.

At present our method for sterilization of the female based upon the work of Béclere and Solomon⁶ consists of x-ray therapy to the ovaries and uterus, applied through the anterior and posterior pelvis in divided doses over a period of several weeks or the insertion of a small quantity of radium into the uterine canal, which is left in place for several days. The divided dose method is more advantageous than the single massive dose because in this method ill effects on the patient of the large dose are avoided, menopausal symptoms appear more slowly, the effect is more certain; overdosage avoided, and the treatment plan and dose may be varied from time to time as the condition of the patient warrants.

Conditions in the female for which sterilization may be indicated can be classed, for convenience, in four large groups: (A) Medical, (B) surgical, (C) gynecological, and (D) social.

Sterilization follows as a necessity when treating malignancy of the generative tract.

I. Reasons for Irradiation.—Irradiation either by means of x-ray or radium is a positive, readily administered, harmless procedure for sterilizing the female. This procedure is the method of choice, because, when properly administered, there is no mortality and no morbidity. Sterilization by x-ray therapy does not necessitate hospitalization as is required for surgical procedures, which may often present innumerable, difficult conditions for the surgeon, while irradiation is often a simple procedure, presenting few difficulties and rarely any adverse sequelae.

Surgical methods, unless that of total extirpation of the reproductive organs, have occasionally been unsuccessful in achieving the final result, because it has been reported that pregnancies occasionally ensued after such procedures. Adequately delivered irradiation will assure the patient definite sterility.

II. When to Select Irradiation.—Assuming that the internist has decreed sterilization to be essential for the patient's welfare in a case with cardiorenal disease or diabetes, irradiation is an effective valuable therapeutic method, because one need not contend with operative shock, infection, bed confinement, and other operative exigencies.

Particular attention is called to pulmonary tuberculosis in females where pregnancy may severely delay recovery or even cause loss of life. Sterilization in such cases is most effective in giving the patient an opportunity to recover. Rather than risk a serious operative procedure when active advanced tuberculosis is present, irradiation certainly is the method of choice for sterilization. In young women with active tuberculosis, where sterilization is decided upon, irradiation may cause cessation of menstruation for only a year or two, and then permit its resumption when the diseased lung condition has been sufficiently ar-

for pregnancies that had followed, and subsequent operation for ovarian cystic disease. Of 223 patients, he had a follow-up of 72 per cent with no pregnancies. However, here is a condition in which practically a 100 per cent of follow-up really exists, for if a pregnancy occurs, the patient immediately reports it to the operator, usually with vindiction!

A few cases have been brought to my attention, claiming failure. One was a patient at the Jewish Hospital of Brooklyn who had an ectopic pregnancy. Inquiry developed that the sterilization attack was not done by the Pomeroy technique. A similar report came from the Methodist Hospital, but I was unable to ascertain the details. Within a fortnight, however, there was reported from the Peek Memorial Hospital an ectopic pregnancy in a woman who had been operated upon by technique identical with ours, I feel quite certain. Kellogg of Boston reported two cases that he did in the course of cesarean sections; he filed elaborate studies of the histology of the removed tubes recovered at second operations. He and I are led to believe that he did not take up a long enough loop of the tube on one side or the other.

With the long series that Lull has reported, more than one hundred at the Brooklyn Hospital and possibly an equal number at the Methodist, and unknown cases from other institutions, I feel that, with inquiry, 500 cases could be found. With only one case of subsequent pregnancy, I believe that we have, for the present, the most satisfactory method, for it is simple, safe and as sure, at least, as is humanly possible.

STERILIZATION BY IRRADIATION*

IRA I. KAPLAN, B.Sc., M.D., NEW YORK, N. Y.

(From the Division of Cancer, Department of Hospitals, New York City and Radiation Therapy Department, Bellevue Hospital)

THE subject of sterilization of the female is of grave importance to the radiation therapist, because of the numerous conditions and lesions associated directly or indirectly with ovarian or uterine physiology which he is called upon to control by a modality that is a newcomer among the customary standardized therapeutic means heretofore employed.

Until the beginning of the twentieth century, surgery was the only means of sterilizing the female. Then closely following the discovery of x-ray and radium, therapists discovered the biologic possibilities of this radiant energy. At first only its destructive qualities were noted, but soon the positive biologic and physiologic effects of x-ray and radium to stimulate or destroy cellular activity were recognized.

In 1904 Halberstaedter¹ based on the work of Albers-Schoenberg² who was the first to produce aspermia in the males by x-ray and that of Bergonie and Tribondeau,³ who formulated the law that immature cells and those in a state of active division are more sensitive to irradiation than are cells which have already attained their adult morphologic and physiologic character, reported his observations with reference to the selective action of x-rays on ovarian tissues, and this developed the logical basis for treatment of gynecologic conditions.

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is present, contraindicating radical surgical procedures. But in young women radium is more likely to cause permanent destruction of the endometrium than does x-ray. In very obese women, x-ray is ineffective because an insufficient depth dose reaches the pelvic organs, and therefore direct radium application in the uterus is necessary to control the condition. In cases where adequate x-ray therapy has failed to effect the desired results, subsequent radium therapy is indicated.

In cases of young females with some general condition necessitating sterilization, irradiation is the method of choice. Assuming a case of tuberculosis, where it is hoped to arrest the chest lesion, temporary amenorrhea would be the ideal aim. In such instances, x-ray therapy alone is advised. Formerly, radium therapy was deemed preferable in young women, since small doses destroyed the endometrium, but spared the ovary to a great extent because of the protection offered by the distance of the uterine canal from the ovary. In our experiments, reported in 1936,⁹ we determined that only about 24 per cent of the radium dose given in the uterus reaches the ovaries. However, whereas menstrual function has quite often been resumed after x-ray therapy, it is more likely to be permanently suppressed following radium therapy.

The effectiveness of irradiation depends upon:

1. *Age*.—The younger the patient, the less the permanency of sterilization, and the older the patient, the nearer she is to the menopause period, the more rapid and permanent the sterilization. Rubinfeld and Maggio,¹⁰ based on the study of a large number of patients treated at Bellevue Hospital, determined the chance of resuming menstruation after irradiation to be, in the age group of twelve to eighteen years, 100 per cent, between the ages of thirty-three and thirty-nine, only 53 per cent and in patients over fifty-three years of age, 0 per cent. The age group between nineteen and thirty-two years usually resumes menstrual function in about 75 to 80 per cent of the cases treated.

2. *Method Employed and Intensity of Dose Administered*.—The more intense the x-ray therapy administered directly to the ovaries and uterus, the more permanent the results. In radium therapy, the amount of dosage, the thickness of the filter used, the length of time employed for the application—all these vary the effect of the irradiation. In our opinion, radium therapy when properly used will more positively sterilize the female than will x-rays. The more intense the given dose, the more positive the results.

3. *Physical Size*.—The stouter the patient, the less intense the radiation reaching the ovaries or uterus. A greater surface dose of x-ray is required in a stout person in order to increase the percentage of depth dose reaching the uterus and ovaries.

4. *Condition of the Pelvic Organs, and Pelvic Infection*.—Where the uterus is sclerotic and small and the ovaries fibrotic, the reaction to irradiation is slow. In multiple fibroids, the effectiveness of irradiation is much lessened because of the multiplicity of the lesion. Extraordinarily large fibroids are but slowly affected by irradiation, yet in many instances irradiation is most valuable for the treatment of large fibroids when surgery is contraindicated. The presence of marked pelvic infection prevents effective reaction on the ovaries and uterus until the inflammatory condition has subsided. In the presence of pelvic infection, pus tubes and pyometria intracavity radium therapy is contraindicated.

rested.⁷ This, to be sure, would be an ideal condition but, unfortunately, it cannot be promised in every instance, although it does occur in a sufficient number of cases to warrant it as a therapeutic measure of real worth.

In women with severe thyroid toxicosis with pregnancy contraindicated, irradiation because of its freedom from shock or other operative exigencies is the method of choice for sterilization.

In leucemia, sterilization by irradiation is the most effective method of treatment.

Although the hormonal relationship is still to be definitely and adequately established, we advise total sterilization in women of menstrual age who have carcinoma of the breast, especially when associated with bone metastases. This procedure is based upon the clinical observation over many years, that patients with breast malignancy, who were unfortunately permitted to go through a pregnancy, had a definite aggravation of the cancer. In recent years, the influence of the estrogenic and lactogenic hormones of the ovary and pituitary upon the breast tissue has been demonstrated by Taylor⁸ experimentally and clinically. Therefore, when it has been decided to sterilize such a patient, rather than submit her to another operative procedure, it is advisable to recommend sterilization by means of irradiation.

Often we are confronted with the problem of a woman over forty-five years of age presenting symptoms suggestive of the climacteric, and serious enough to necessitate operative intervention, with hormone therapy proving valueless. In such conditions irradiation is effective and harmless in relieving these symptoms, especially the profuse metrorrhagia which sometimes characterizes such changes in the female.

When, in occasional instances, an endometriosis is encountered, irradiation can be administered to the ovaries, and thereby inhibit endometrial activity at the site of the neoplasm. This method is superior to operative removal of the tumor mass along with ovariectomy. With irradiation sterilization, there is no associated operative risk nor mortality.

III. *Methods and Technique.*—a. X-ray therapy is the most feasible method to employ for sterilization. Patients can be treated ambulatory with little distress and minimum amount of disturbance.

b. Radium therapy may be employed, but in most instances this requires hospitalization. X-ray therapy is the treatment of choice in such conditions where any type of surgical procedure is contraindicated, and therefore radium therapy, entailing the introduction of radium into the uterus, a surgical procedure, may not be employed.

c. In those conditions where patients are close to the menopause, in the case of thin patients and in those who for economic reasons cannot afford the necessary hospitalization required by radium therapy, it is better to employ x-ray therapy.

d. X-ray therapy is used for temporary sterilization in young women or where temporary amenorrhea is required for relief of local or general conditions, because of the greater ease in controlling the administered dosage. At present, we have definite physical means of measuring a specific unit of x-ray dosage under standard conditions.

The use of radium is advised where bleeding is profuse and there is immediate, urgent need to arrest hemorrhage, and where severe anemia

Irradiation sterilization is of equal worth and effectiveness with surgery, without the latter's associated mortality and morbidity.

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55 EAST EIGHTY-SIXTH STREET

STERILIZATION FROM THE POINT OF VIEW OF THE OBSTETRICIAN AND GYNECOLOGIST*

B. P. WATSON, M.D., NEW YORK, N. Y.

MY VIEWS on this subject can be best and most briefly expressed by presenting to you an analysis of the public ward cases in which sterilization has been carried out in the Sloane Hospital for Women during the past five years, 1931 to 1935 inclusive. During these years we have sterilized 172 women: 44 in 1931, 28 in 1932, 46 in 1933, 27 in 1934, and 27 in 1935. This gives an average of 34 per year. The average for the four years 1921 to 1924 was 13.6. It is thus evident that we are sterilizing more women today than we were ten and fifteen years ago.

The total number of deliveries in the public wards of the Sloane Hospital for Women averages 1,575 per year. This gives a case incidence for sterilization over the past five years of approximately 2.17 for every one hundred patients delivered.

Indications for Sterilization.—In 28 per cent of the cases the patients were sterilized primarily because it was not desirable that they be subjected to future cesarean sections. Thirteen per cent of the cases were from the gynecologic wards and sterilization accompanied a plastic operation. In 20.4 per cent sterilization was done because of toxemia of pregnancy, including nephritis and hypertension, and in 14.4 per cent because of heart disease. The heart disease in these cases was chiefly of the rheumatic valvular type, although a few cases of syphilitic heart disease and one case of congenital heart disease are included. In 8.4 per cent the indication was of a neuropsychiatric nature. Among these are included several cases of psychoneurosis, psychosis, mentally defective individuals, grand mal, one case of multiple sclerosis, and one of disseminated sclerosis. In 4.2 per cent tuberculosis of one sort or another was the indication. In 2.4 per cent it was diabetes. There were two cases of central nervous system syphilis. In the remaining cases there was a variety of indications; in two a previous nephrectomy had been

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Complications.—These may be due to: (1) Condition within the patient, (2) errors in technique, and (3) untoward effects.

1. Occasionally, radium application is made in the uterus when an unrecognized latent pelvic infection is present, lighting up the infection with subsequent formation of salpingitis and, in some instances, peritonitis. An unrecognized pregnancy may be aborted or the embryo destroyed in utero with the formation of pyometritis.

2. Errors in technique may cause distressing or even fatal conditions. Too intensive a dose, or x-ray improperly administered, may result in superficial burns of the skin, epilation of pubic hair, telangiectasis, and fibrosis of the abdominal wall. In some instances intestinal disturbances, colitis or proctitis, may occur. These may sometimes be ulcerative in character.

Poor or careless technique when radium is inserted into the uterine canal may result in perforation of the uterus. Should this occur accidentally, the radium is withdrawn and the patient treated expectantly. If the radium procedure has been carried out under aseptic conditions, healing takes place without further disturbance. If the dose is too intense and the radium improperly applied, fistulas into the bladder or rectum may occur; proper placement of the radium applicators and careful packing of the vagina will militate against such sequelae.

3. In some cases, sterilization intended as a temporary measure may create permanent amenorrhea and sterility, and the patient should always be told of this possibility. In a few instances irradiation sterilization may result in a too rapid onset of the menopause. In such cases, irradiation over the pituitary may relieve the distressing symptoms associated with menopause changes.

Radiation Sickness.—No matter what method of irradiation is employed, radiation sickness, nausea, vomiting, and malaise, may occur in some cases. Its cause is not as yet understood nor is it known why it should occur in some patients and not in others. Dietetic control, citric acid fruit juices, calcium gluconate, liver extracts, sedatives such as luminal or nembutal, atropine and sodium bicarbonate, are all useful in treating this condition. In some instances, symptoms are so severe as to require rectal feedings or intravenous infusions. Roentgen sickness, though at times very distressing to the patient, is rarely fatal. It ceases with the conclusion of the irradiation.

CONCLUSIONS

When properly administered by an experienced and trained therapist, sterilization by irradiation is effective and at the same time produces no untoward effects. Occasionally, irradiation sickness may occur, requiring special attention, but this condition is relieved with cessation of the treatment. When radium is employed, proper surgical precautions are essential to prevent infection or perforation. Radium therapy must not be administered in the presence of adnexal infection.

In young women, sterilization may be permanent instead of temporary and in some cases sterilization by irradiation may not prove effective, requiring subsequent surgical procedures.

To obtain effective results, it is essential that irradiation sterilization be carried out only by those properly prepared by training and experience in the employment of x-ray and radium therapy.

advised against sterilization; but, if after due consideration she and her husband still insist, her request would be acceded to. The advice against sterilization at a first section is, however, usually taken, for in the 23 cases in which such sterilization was done, definite indications against future pregnancies were present as follows: toxemia of various types 8; heart disease 8; tuberculosis 2; and one each of hydro-nephrosis, diabetes, mental defect, previous plastic operation in a para iii, and placenta previa in a para iii.

The choice of sterilization at the time of the second and third cesarean sections was much more freely exercised. It was done in 21 cases at the time of the second, and in 26 at the time of the third, section. In most of these patients there was present only a mechanical impediment to normal delivery and no pregnancy complications, so that sterilization was done simply to protect them against the risk of a future laparotomy.

The method of sterilization adopted in these cases of cesarean section varied; in some it was resection of the tube; in others subtotal hysterectomy. I believe that the latter is the procedure of choice if the patient will consent. It does not take longer to do than suture of the uterine wound and tubal resection, there is less blood loss, and the convalescence is easier and safer, for the organ in which infection is most likely to develop has been removed.

Provided the patient has not a "sentimental attachment" to the menstrual function, most of them will consent to this procedure if a little time is taken to explain to them that if they are to have no more pregnancies, the uterus is a useless organ, and that its removal will in no way unsex them. In my experience removal of the uterus does not tend toward an earlier menopause.

Sterilization at the Time of Abdominal Hysterotomy.—In the second group of cases, sterilization was done at the same time as a hysterotomy for the removal of an ovum before the period of viability. After fourteen weeks of gestation, we believe that the removal of the ovum is more safely accomplished by hysterotomy than by any method of dilatation or packing of the cervix. Vaginal hysterotomy is the method of choice in such cases if sterilization is not indicated, abdominal hysterotomy if it is indicated. Sterilization by resection of the tubes through the vaginal fornix can be done and is done by some operators at the same time as a vaginal hysterotomy. I personally do not like it as the blood loss from the incision of the cervix and the emptying of the uterus obscures the operative field and so very often renders the operation "sloppy."

In those cases beyond three and one-half months then, we regard the sterilization as an incident in the course of terminating the pregnancy by abdominal hysterotomy. But in 44 per cent of our cases of hysterotomy and sterilization, the pregnancy had not advanced beyond the second month. In these the pregnancy could have been easily and safely terminated by a simple dilatation and curettage. It might be said of them that the hysterotomy was an incident in the course of the operation for sterilization, the opening of the abdomen being necessary only for the latter procedure.

Little need be said regarding the third group of cases, those in which some gynecologic plastic operation had been carried out; a high amputation of the cervix, the repair of a large cystocele or rectocele, the repair of a long-standing third-degree tear, the repair of a bladder or rectal fistula, all of these render future childbearing undesirable. All of these women have borne children and in most of them the operative procedures are not done until they have acquired what they consider a sufficient family. If there is any doubt as to their capacity to use some contraceptive device, or if they are unwilling to do so, sterilization is indicated.

I am not going to discuss the technique of sterilization further than to say that in those cases in which hysterectomy is not done, I personally

done, two were cases of malnutrition and there was one of each of the following: nephrosis, recurrent nephrolithiasis, previous pyelonephritis, hydronephrosis, ulcer of stomach, stricture of rectum, anemia with splenomegaly, hyperemesis gravidarum with syphilis, recent pleurisy with syphilis, and obesity in a para viii. As will be stated later on, in all of these patients, there were other definite indications for a laparotomy.

In connection with these figures and in comparing them with statistics from other hospitals, it should be remembered that the Sloane Hospital is a voluntary and a teaching hospital, and that in selecting cases for admission, preference is given to those which exhibit some abnormality. The circumstances under which these 172 women were sterilized were as follows:

1. At the time of cesarean section in order to protect the patient from the risk of future sections, or from the risk entailed by future pregnancies, in the presence of some condition, such as heart disease, which rendered the first section necessary, 41 per cent.

2. Along with hysterotomy in patients in whom, because of some complication, it was deemed wise to terminate pregnancy in the early months and in whom any subsequent pregnancy would entail an equal or greater risk, 46 per cent.

3. As part of the procedure in extensive plastic operations on the cervix and pelvic floor accompanied by suspension of the uterus, 13 per cent.

In only one case was sterilization deliberately done as a procedure per se in the absence of pregnancy or other gynecologic operations and in that one the x-ray method was used. In all the others sterilization was performed in conjunction with other operative procedures, notably cesarean section and hysterotomy.

Such a policy could not have been followed had we not had a contraceptive clinic to which we could refer all patients presenting any condition rendering future pregnancies dangerous. The contraceptive advice there given has saved many women from operative sterilization. However, quite a number who have received instruction have, usually because of carelessness, become pregnant and they constitute quite a large percentage of the hysterotomy and sterilization cases.

If contraceptive advice has been given to a patient on a sufficient indication and she subsequently becomes pregnant, therapeutic abortion is usually advisable. As her failure to prevent this one pregnancy is presumptive evidence of future failure, she is given the option of surgical sterilization at the time of the operative termination of the pregnancy. It is our experience that the average clinic patient is less able or less willing to carry out contraceptive technique than is the average private patient, so that sterilizing operations are more often called for in the former than in the latter.

We shall now take up in detail each of the three groups of cases mentioned above:

1. *Sterilization at the Time of Cesarean Section.*—Seventy-one cases. The indications for sterilization in these cases were: (a) To prevent the risk of a subsequent section; (b) the presence of some condition rendering future pregnancy hazardous. I personally believe that a woman has the right to ask for sterilization at the time of a first cesarean section. If the section has been done because of pelvic abnormality or other conditions which simply prevent normal labor, and there is no condition present which would render subsequent pregnancy dangerous, she is

LEGAL CONSIDERATIONS FOR THE PHYSICIAN*

WILLIAM J. McWILLIAMS, NEW YORK, N. Y.

(*Attorney-at-Law*)

THE State of New York and nineteen other states in the United States have no statutes relating to human sterilization. The other twenty-eight states of the Union have laws providing for either compulsory or voluntary sterilization of mentally deficient or unfit persons, and pursuant to these laws at least 23,118 operations have been performed. Among these twenty-eight states there are four (Connecticut, Iowa, Kansas and Utah) that limit sterilization in private medical practice to cases where the performance of such operation is a "medical necessity."

An examination of all the varied relationships between the law and human sterilization is a subject too wide for this brief symposium. But the topic uppermost in the minds of most physicians may be stated in these terms: What is the civil and criminal liability, if any, of the operating physician in private practice in the United States who performs a vasectomy or salpingectomy? This limitation of the question makes possible a brief discussion of the major legal considerations important to the operating physician.

The first consideration in private practice in all cases is to obtain a consent to the operation from the patient. Judge Cardozo, now in the United States Supreme Court, stated the rule as to civil liability applying to all surgery, in these words: "A surgeon who performs an operation without his patient's consent commits an assault for which he is liable in damages . . . except in cases of emergency where the patient is unconscious. . . ."

Likewise, if the operation were performed without the patient's consent, it would constitute criminal assault, as well as civil.

A proper perspective in applying the law to sterilizations may be kept if familiar types of sterilization cases are first considered. The report made here this evening of work done at various hospitals shows that medical indications may require the removal of the uterus or the ovaries, or the severance of the fallopian tubes or of the vas deferens as an incident to the cure or prevention of disease. In such cases the usual routine hospital consent from the patient to operate is a complete shield to the operating physician against civil and criminal liability, even though the power to procreate has been destroyed, provided the operation is performed without negligence. Nobody is even mildly surprised at such operations or at the law. They are everyday medical experience.

But suppose the sterilization of either the man or woman is solely for eugenic purposes?

Recently a brilliant professional man disclosed to his physician in New York a family history of physical disorder and mental disease

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prefer resection of the isthmie portion of the tube, covering the proximal end accurately with the peritoneal folds of the broad ligament. I may have had failures by this method but none have so far come to my notice. In our present hospital series, two patients became pregnant subsequent to a supposed sterilization, one by resection of the cornu and one by resection of the middle third of the tube. The following gives the percentages of the various procedures used by all members of the staff: (1) Ligation and resection of middle or isthmie portion, 54 per cent. (2) Resection of cornu, 21.4 per cent. (3) Pomeroy, 15 per cent. (4) Hysterectomy, 9.4 per cent. (5) Radiotherapy, one case.

From this brief summary, it is evident that in the Sloane Hospital sterilization is done in the majority of cases for conditions which render further childbearing hazardous to the mother. In only a small minority has it been done for eugenic reasons. The explanation for this is to be found in the comparatively small number of cases in the latter category which came under observation. When a definite eugenic indication is present, we believe sterilization is in order.

Finally, sterilization is called for in any case only because contraceptive methods are still imperfect. When a method, biologic or other, is evolved which is 100 per cent certain, and which does not emotionally upset either partner, sterilization will be unnecessary.

As surgical sterilization of the male is an easier and much less hazardous operation than that of the female, it might be thought that many devoted husbands would choose to have this done in order to save their wives. In my whole professional experience only one, and he a medical man, has made this choice.

tioned, Connecticut, Iowa, Kansas and Utah, where it has not yet been decided by the courts whether such case would come within "medical necessity." These states will probably follow the Minnesota ruling above mentioned.

Suppose a woman, in order to remove the dread of unfit children or of dangerous pregnancy, goes to a physician and is sterilized without notifying her husband. In the few cases that have been considered, it is agreed that if the wife's consent is obtained, the consent of the husband is not necessary. If the husband's consent is not necessary for an operation on the wife, her consent should not be necessary for an operation on him. However, a prudent physician can avoid any question on this point by requiring both to join the consent, which should contain a plain statement of the nature and effect of the operation.

Suppose a patient under twenty-one years of age requests a salpingectomy or vasectomy for therapeutic or eugenic purposes; let us say, a boy or girl in the teen age. Such cases are not uncommon. If the purpose of the sterilization is therapeutic and incidental to the treatment of the patient's disorder, then the consent of at least one of the minor's parents or of the minor's guardian must be obtained before the operation is performed, and it would be advisable for the physician to obtain the consent of the minor where such minor is old enough to comprehend the operation.

However, if the proposed sterilization of a minor is for eugenic purposes, then the minor should be required to join with at least one of the parents, or the guardian, in the request and consent for the operation, and the physician should make very sure that the minor comprehends the nature and result of the operation.

If the minor happens to be married or emancipated from his or her parents, then such minor may be treated like an adult, although prudence on the physician's part would cause him to get consent of both parties to the marriage before operating on the minor spouse.

Finally, suppose the patient is a mentally defective person who has not been judicially declared incompetent. The physician in private practice who sterilizes a person of this class incurs a risk of civil, and possibly criminal, liability because the validity of the patient's consent may later be challenged. The physician must be prepared to show that such mentally defective patient had sufficient intelligence to understand that he or she could not beget children after the operation was performed, and requested the operation.

It is for the special benefit of mental defectives that many states have passed sterilization laws. The most highly regarded and widely used statute of this kind is in California. It provides that sterilization by vasectomy or salpingectomy is a prerequisite to the release of mentally defective persons who have been committed to state institutions, and it also provides for voluntary sterilization upon request of parent or guardian of a mentally defective minor or an incompetent adult. Vermont has another type of sterilization law providing for voluntary sterilization of adults or minors who are mentally defective, but the law contains no compulsory features. The Virginia statute, famous for being upheld by the U. S. Supreme Court in *Buck vs. Bell*, is entirely compulsory in its provisions and covers mentally defective persons in state institutions.

through two generations of ancestors and extending to his brothers and sisters, although the patient was apparently normal. The physician agreed with the patient that his offspring were likely to inherit the same disorder, and upon the patient's request performed a vasectomy. This was proper action on the physician's part. It is lawful in New York and probably in all states for a physician to perform a vasectomy or salpingectomy in private practice on a sane adult for the eugenic purpose of preventing procreation of children likely to be mentally defective or unfit. Possible exceptions to this general rule might arise (though it seems unlikely) in Connecticut, Utah, Kansas and Iowa, under future judicial interpretations of what is meant by "medical necessity" as contained in their special statutes limiting private sterilizations.

In the New York case just mentioned, the general criminal statute of the State covering maiming or mayhem does not apply, because the essential element of criminal intent to injure or maim is entirely lacking on the part of the physician. Further, there is no legal duty in the United States to have children, so the patient is not evading a civil obligation. The intent and purpose of the operating physician is the same as purpose approved in the famous case of *Buck vs. Bell* (274 U. S. 200) in which the Supreme Court of the United States held constitutional a Virginia statute compelling sterilization of feeble-minded persons for eugenic purposes. This case of *Buck vs. Bell* definitely established the propriety of eugenic legislation. The constitutionality of laws providing for the sterilization of the unfit has been established in a number of states.

Now suppose the requested sterilization by vasectomy or salpingectomy is sought solely to remove danger of pregnancy of the wife? This type of case was considered by the Supreme Court of Minnesota in 1934 (255 North Western Reporter 620). A husband had himself vasectomized for the protection of his wife against another pregnancy. The operation was unsuccessful; the wife delivered a healthy baby. The husband sued the surgeon for damages. The surgeon, among other defenses, set up the novel plea that the performance of a sterilization operation on a healthy man was contrary to public policy and therefore illegal. The court found against the plaintiff on general grounds, but concerning this plea, the Court said, "Aside from the statutes in the few states that have prohibited it, we find no judicial or legislative announcement of public policy against the practice of sterilization. Certainly even in those states with statutory prohibition the exception of medical necessity would justify the physician in performing the operation here alleged. Plaintiff was married and presumably would remain married to his present wife, who had been competently advised of the danger of further pregnancy." (Rather than subjecting the wife to an operation for sterilization.) "It was entirely justifiable for them to take the simpler and less dangerous alternative and have the husband sterilized. . . . We therefore hold that under the circumstances of this case the contract to perform sterilization was not void as against public policy, nor was the performance of the operation illegal on that account."

It appears that there is no legal hindrance in private practice to performing a vasectomy for the purpose of preventing pregnancy in the patient's wife, except possibly in the four states previously men-

Further, sterilization of the feeble-minded is easy to advocate. We believe that 90 per cent of the cases of feeble-mindedness show hereditary influence. In this matter we are undoubtedly breeding from the bottom, and we spend six times as much bringing up one mentally defective child as we do a normal child. Further, it would seem somehow proper that the group that pays for the support and upbringing of the offspring of defective individuals should have some say regarding their multiplication. However, there are five or six times as many cases of minds somehow disordered, outside institutions as in them. If we could devise a fitting standard for feeble-mindedness, that is if we can catch the feeble-minded and properly christen them—and there's the rub—I believe we can properly sterilize them.

In fine, sterilization of the feeble-minded, if done largely and thoroughly, would, I believe, aid our civilization. Sterilization of manic depressive individuals might add to the human happiness of our immediate future, but almost certainly would slow up advancement of humanity in the long view. One day we will know more; then perhaps we can act firmly.

Men die, the ordered detail of each successive civilization dies, but from each wreck a thought, a theory, a conception of beauty, is saved, and serves as a torch to light the ways of men who seek again to build up the edifice of human society. Our knowledge is not quite sufficient to tell us what kind of mind will come from a particular kind of body, strong or ill. We can as yet only breed from the physical standpoint; and uniform physical perfection may contribute little, from generation to generation, to the advancement of thought or beauty, or the love of knowledge.

410 EAST FIFTY-SEVENTH STREET

STERILIZATION FROM THE STANDPOINT OF THE INTERNIST*

JOHN WYCKHOFF, M.D., NEW YORK, N. Y.

(From the Department of Medicine of the New York University Medical College)

THE interest of the internist in the subject of sterilization must be an interest which is broader than the effect of pregnancy upon chronic disease. It must include the effect of pregnancy on the patient who has chronic disease and that patient's environment, and also the effect of sterilization upon a woman of childbearing age who has no chronic disease. From the arrangement of this program I assume that others will discuss the various methods of the prevention of pregnancy. For these reasons I will limit myself as far as possible to discussing pregnancy as it affects the mother and child in chronic disease. I say chronic disease, for in acute disease it is difficult to think that permanent sterilization would ever be indicated. Such impressions as I shall give will be the impressions gathered by our staff at Bellevue.

I will speak first of pregnancy in the course of chronic diseases of the blood-forming organs. Numerous reports of successful pregnancy

*Read before the Section on Obstetrics and Gynecology, New York Academy of Medicine, November 24, 1936.

STERILIZATION AND EUGENICS*

FOSTER KENNEDY, M.D., F.R.S. (EDIN.), NEW YORK, N. Y.

(From the Department of Neurology, Cornell University Medical College)

IN THIS sphere of thought it is easy to be dogmatic, difficult to be right. For only fifty years has man been conscious of his own evolutionary development, and already many begin to realize that he will soon reach out toward conscious direction of that development. It is doubtful if as yet our brains are big enough, or our knowledge deep enough, to direct properly so gigantic an adventure. We would seem to have achieved our unique position of supremacy in the animal world by some inner power forbidding us, at any evolutionary crossroads, to take the path of specialization. We can see, but less well than an eagle—hear and jump, less well than a cat—swim less well than do fishes, and jump nimbly in the tree tops less well than our ancient collateral cousin, the ghostly Tarsius. If we really were to succeed in breeding for perfection as we do milk cows, we would be tempted to specialize, and to what end would we do so? What quality would we pick? Our figures show that of the children of a manic depressive, mated to a normal, one-third are manic depressive and of the children of a manic depressive mated to a manic depressive, two-thirds have the disease. One might say that this is prima facie evidence for sterilizing manic depressive individuals; but again one must look at the question from another point of view. We do not advance from century to century, from civilization to civilization, by reason of the mass of mediocre people, but by the ideas springing from the minds of the brilliant few. These brilliant few have often been eyethymic persons who, afflicted often in their lives by periods of desperate depression, illuminate the world by flashing thoughts which come when energies and mental quickness are enormously increased during their periods of elation.

Sparta practiced infanticide more widely than other states for a military end. The Laeadaemonians were perfect, as a pack of wolves is perfect, but the glory of Grecian thought did not come out of Sparta. Julian Huxley has lately pointed out that it is improbable that human altruism will very greatly increase unless we entirely change our habits of procreation, setting aside individuals solely for this purpose, as do the insects, who have established thereby a rigid caste system. It is surely doubtful if man is ready to act on biologic truth when he is clearly content politically to live under a biologic lie. Germany at present has ordained that persons with schizophrenia and manic depressive insanity should be sterilized. When we consider that no man living knows anything of the pathology underlying these two conditions, it would seem premature and improper to lay unwitting hands upon them. However there is something to be said for the idea, not just of sterilization, but of castration of the criminal insane, in that eunuchs retain their intellect but lose initiative and emotionally are ideal seconds-in-command.

*Read before the Section on Obstetrics and Gynecology, New York Academy of Medicine, November 24, 1936.

essential hypertension; (2) the influence *on* pregnancy of glomerulonephritis, essential hypertension and previous toxemia of pregnancy.

Active glomerulonephritis is a distinct contraindication to pregnancy. This is especially true when renal function is impaired. It is almost invariable that when a young woman with active glomerulonephritis becomes pregnant, in the first trimester there occurs an increase in proteinuria and hypertension. The mechanism is most likely a further degree of angiospasm on already sensitive arterioles. While there is no clear evidence to indicate that this type of exacerbation results in persistent further loss of renal function (as occurs in true inflammatory exacerbations of glomerulonephritis), there is great danger of permanent retinal damage with loss of vision consequent on the rise of blood pressure. On the other hand, glomerulonephritis in the latent state, i.e., proteinuria without hypertension or functional insufficiency, is no contraindication and such individuals are apparently no more susceptible to untoward occurrence than otherwise normal women.

Uncomplicated essential hypertension is rarely a contraindication to pregnancy. Most women with this condition go on to term or to the period of viability without the slightest difficulty. While such individuals are more prone to angiospasm in pregnancy and consequent increase in blood pressure than normal women, it most often occurs after the sixth month so that many can be carried to the period of viability if not to term. Moderate rises in blood pressure which may occur in these women tend to disappear rather promptly after delivery.

When essential hypertension is complicated by retinal hemorrhages and areas of degeneration, when before pregnancy the diastolic pressure is very high (120 mm. Hg or more) or when functional tests show distinct loss of kidney function, women should not become pregnant. Myocardial involvement due to coronary disease or previous cerebral accident, both of which might be influenced by a further rise in blood pressure, should also be considered contraindications.

In active glomerulonephritis, pregnancy rarely, if ever, goes to the period of viability. The frequent appearance of superimposed angiospasm in the first or second month leaves too long a period of morbidity. The rule is early miscarriage.

In uncomplicated essential hypertension in which the diastolic blood pressure is not above 100 mm. Hg, it is the rule for pregnancy to be entirely normal. When the diastolic blood pressure rises well above this, it is often necessary to induce labor shortly before term, since premature separation of the placenta may occur and result in a stillbirth.

Prediction as to the effect of a previous "toxemia" on subsequent pregnancies depends upon two observations: (1) the interval examination; (2) the number of previous "toxemias." If the patient makes a prompt recovery after delivery and over a period of one year there has been no recurrence of hypertension, she may be allowed a second pregnancy with little fear of serious recurrence. However, regardless of how prompt recovery was, the reappearance of even a mild grade of persistent hypertension makes the chance for recurrence great (about 60 per cent).

If the patient has had two successive "toxemias," it is the rule for recurrence to occur in subsequent pregnancies. While there are exceptions to this rule, there is no certain way in which such exceptions can be

in patients suffering from chronic leucemia have appeared in the literature. One of Dr. Connery's patients discovered that she had leucemia while she was pregnant. A living child was born and as far as we could determine the patient lived the natural span of the disease. Another patient with chronic leucemia, probably the youngest in our series, passed a complete and successful pregnancy years after the diagnosis of leucemia had been made. The disease ran one of the longest courses we have ever seen.

During the course of pregnancy, anemia of several types and of varying degrees of severity is frequently seen. In almost all instances, this anemia may be relieved by diet or by iron or by a combination. Macrocytic hyperchromic anemia of the Addisonian type can be successfully treated. There are several reports showing increased life span in patients with pernicious anemia, when the treatment is adequate. I know of no reports that show that the course of the disease is shortened by the occurrence of pregnancy, or where the children born of such a mother were inferior.

In congenital hemophilia we have a different problem. A woman with the hemophilic taint in her blood bears children with great risk of transmitting to some of them a disease which at present can be treated only incompletely, and to all such children genes which may be transmitted to subsequent generations.

Hyperthyroid disease, being of frequent occurrence in women during the childbearing period and because of the effect of pregnancy in increasing the degree of hyperthyroidism, presents a definite problem. Patients with uncontrolled disease should not become pregnant. Many cases controlled either by Lugol's solution or operation complete pregnancies successful to both mother and child. Patients with hyperthyroidism who have true heart disease do very badly and should not become pregnant.

Diabetes per se is no contraindication to pregnancy. If a diabetic patient, however, should be unable to avoid repeated pregnancies, pregnancy would be contraindicated, as in the latter part of pregnancy the diabetes is likely to become very severe. Skipper recently discusses the question and says that each case should be judged individually. In making a decision he feels that such considerations as the economic condition of the patient, the number of children in the family already, and the mentality of the patient are important considerations because of the tendency of diabetes to occur in families. Some observers feel that childbearing in diabetic patients should be limited because of the possibility that in the future the child may develop diabetes. This obviously involves a discussion that would be endless, and I mention it because it is one of the points that occasionally is brought up.

There seems to be little in maladies of the digestive tract to indicate sterilization. These diseases of themselves are not hereditary. Peptic ulcer is not generally thought to constitute much of a hazard in pregnancy. Dr. Lockwood used to think that remission was the rule in pregnancy and Crohn says in his *Affections of the Stomach* that "conservative treatment of an ulcer during pregnancy is very promising." It is possible that vomiting of pregnancy might increase the ulcer risk but that would hardly be an indication for sterilization of the woman.

Renal disease and hypertension have to be considered from two aspects: (1) the influence of pregnancy on glomerulonephritis and

tuberculosis knows that there are chronic active cases with extensive lesions who, one may be sure, will never become inactive and in whom pregnancy should never be allowed. There is also the type of patient who has exacerbation of symptoms frequently with her menstrual period. Such cases, it is believed, have a much better chance of cure if an artificial menopause is brought about.

I have spoken of hemophilia, Graves' disease, active glomerulonephritis, previous toxemias of pregnancy, certain types of heart types, and certain types of tuberculosis, when occurring in women at the childbearing period, as being contraindications for pregnancy. In some of these, pregnancy could probably best be avoided by sterilization, but this should never be done in any case until all complicating factors are considered.

In avoiding the deleterious effects of pregnancy in certain forms of internal disease one must think of four things: the prevention of pregnancy by continence or contraceptives, or the prevention of pregnancy by sterilization, either temporary or permanent. The physician who advises permanent sterilization takes a serious responsibility. In general it would seem to me that the indications would be two: the first is where the woman carried an hereditary taint which she is certain to transmit, an example of which would be hemophilia; the second would be a form of chronic disease in which pregnancy or the additional burdens subsequent to childbearing will have serious deleterious effects upon either mother or child, or both, and in which there is practical certainty that the disease itself is either progressive or that it will never improve so as to safely allow a pregnancy. Examples of such indications would be in certain forms of the heart diseases and of tuberculosis.

DISCUSSION

DR. WILLIAM P. HEALY.—The eugenic side of the question seems to have, at least from the standpoint of the neuropsychiatrist, a very slender thread on which to hang. Certainly Dr. Kennedy takes little interest in it.

It is of interest that in the five years' work which Dr. Watson reported in an institution which handles so many abnormal maternity and gynecologic problems, in only 2 per cent did any question come up of the desirability of sterilization. That in itself must surely indicate that the question of sterilization, in obstetrics and gynecology, is one which we do not meet very frequently.

If we review what has been said here tonight, we can conclude that there are three factors which are closely related—contraception, therapeutic abortion, and sterilization. Contraception is very common and much sought after. Therapeutic abortion is willingly accepted. Sterilization is rarely desired. The question of sterilization is the important one and one that we will carry out in a relatively insignificant number of instances, as has been illustrated this evening by Dr. Watson.

We must bear in mind that there is a definite distinction between sterilization, so-called, induced by means of radiation therapy, and sterilization brought about surgically. With the use of radiation, you are very likely to bring about permanent castration with all the associated disturbing symptoms, whereas surgical sterilization does nothing but interfere with the possibility of conception. Therefore, one would hesitate to recommend that a young woman be sterilized by radiation methods, unless a surgical procedure, in itself, be too grave a procedure for that particular case.

Temporary sterilization with radiation therapy may be indicated, in certain conditions, largely of a neurotic type, in which we wish to observe whether certain mental

predicted. The danger of permitting recurrent toxemia is evidenced by the latest available statistics (Herrick and Tillman) that about 50 per cent of these women develop persistent hypertension in the future.

The following quotation is from a report of the American Committee on Maternal Welfare, May, 1935: "Eclampsia and the forms of toxemia associated with it cause annually about 30 per cent of the approximately 15,000 maternal deaths in this country."

In rheumatoid arthritis, pregnancy is contraindicated not because of danger to the patient's life but because our present means of combating the disease consist almost wholly of conserving the patient's strength, and the increased burden of motherhood unavoidably adds to the patient's duties and responsibilities. It has been remarked by a number of writers that during pregnancy itself the patient with rheumatoid arthritis may appear to have a remission so that the impression has arisen that pregnancy may even be beneficial. However, it is my belief that in the long run this is not the case and that even those women who appear to improve during pregnancy are ultimately more likely to run an unfavorable course. On the other hand, I know two women with severe deforming arthritis who had successful pregnancies. They were both economically so situated as to care for themselves.

The heart diseases which occur during woman's fertile period are usually rheumatic; occasional cases of congenital heart disease may be a problem. The bacterial forms of heart disease, because of their acuteness, would hardly ever call for sterilization. Syphilitic heart disease might occasionally become a problem.

Cases of congenital heart disease usually do well if there is little or no diminution of the cardiac reserve before pregnancy. Those with cyanosis are likely to lose their babies. When there is marked diminution of cardiac reserve, pregnancy would be contraindicated. Such cases are rare. All that I have seen have done well.

Patients (inactive) with rheumatic heart disease with good reserve handle pregnancies rather well. I know of no evidence that pregnancy tends to be associated with increased occurrence of activity.

Patients inactive with greatly diminished reserve should not become pregnant. Such patients usually do not have intercourse but if they do, pregnancy should be prevented. Patients with active rheumatic heart disease nearly always have diminished cardiac reserve and while usually they live through a pregnancy they are liable to lose the child. Such patients should not become pregnant. However, many of these patients are active only temporarily and a number become inactive and develop sufficient reserve to go through a pregnancy. The question of advising sterilization in these cases, except the very obvious chronically incapacitated, places a great responsibility on the physician.

Last, an occasional woman may develop a syphilitic aortitis in her late thirties with signs of greatly diminished reserve, usually associated with signs of coronary thrombosis. Such cases do badly. Antisyphilitic treatment often is of no help. Their progress is rapid, the expectancy of life usually being under five years. Such patients should not become pregnant.

My own experience with tuberculosis is meager. It is well known that patients with active tuberculosis are made very much worse by pregnancy. It is also well known that many chronic active cases may cure and become arrested cases, but everyone who has had experience with

Correspondence

Experiences With the Visscher-Bowman Pregnancy Test

To the Editor:

An article entitled, "The Chemical Determination of Pregnancy" was published about two years ago in which the authors, Drs. Visscher and Bowman, described a procedure which by chemical means determined the presence in the urine of the same substance which was found by biologic methods in the mouse or rabbit test.

We have done a total of 112 tests by this method, of which 94 were in known pregnancies and 18 in known nonpregnancies. Of the 94 pregnancies, 82 gave positive tests and 12 negative tests, or a percentage of error of 12.7 per cent. Of the 18 nonpregnancies, 7 gave positive tests and 11 negative tests, or a percentage of error of 38.8 per cent. In the total of 112 cases, there were 19 incorrect results, or a percentage of error of 16.9 per cent.

It would seem fair to conclude that this high percentage of error in a test of this type precludes the possibility of a practical value in the procedure.

SAMUEL B. SCHENCK, M.D., AND IRVING TRAN, M.D.

135 Eastern Parkway,
Brooklyn, N. Y.
June 21, 1937.

Roentgen Diagnosis of Triple Pregnancy

To the Editor:

In the August, 1936, issue of the JOURNAL I reviewed the literature on triple pregnancy diagnosed by x-ray, giving a short summary of the nine cases reported and adding a tenth case from my own practice. At that time I overlooked one case reported by Greenhill in *Medical Clinics of North America*, September, 1923, and 2 cases reported by Weil in *Gynécologie et Obstétrique* for October, 1935. E. W. Titus also reported one case in the April, 1937, issue of the JOURNAL, thus bringing the total number of cases reported to 14. I would like to add the fifteenth case, a patient recently delivered on the Obstetrical Service of the University Hospital, University of Maryland School of Medicine.

H. S., colored, aged fifteen years, single, primipara. The family history is interesting in that her maternal grandmother had 2 sets of twins and one maternal great grandmother had one set of twins. The patient's past history was negative. Her last menstrual period was Aug. 20, 1936, making her estimated date of confinement May 27, 1937. She was first seen in the Out-Patient Department on Nov. 13, 1936 at which time she was thought to be about sixteen weeks pregnant. Kolmer 4-4 was repeated with the same result, weight 112½ pounds, pelvic measurements were slightly less than normal but not enough to cause any concern as we deliver a large number of small colored girls in the clinic without difficulty.

Her prenatal course was normal except for an elevation of blood pressure to 132/78 on December 14 and 132/98 on March 29. She was rather uncooperative about reporting for antisyphilitic treatment and received six treatments only at irregular intervals. The patient was examined on March 29 and because of the marked

disturbances associated with the menstrual epoch disappear when the menstrual periods are diminished. If the symptoms no longer occur when there is amenorrhea, and on the return of the menstrual periods the symptoms recur, then one may go forward with permanent sterilization.

DR. HOWARD C. TAYLOR, JR.—The attitude of most people toward the subject of eugenic sterilization is dependent upon an emotional bias, quite outside the facts of the subject itself. We find perhaps three types of individuals. One group is almost ecstatically enthusiastic. These include the popular scientists, who believe that most of man's ills can be gradually eliminated by a careful selective program. They publish articles in a few scientific journals and in a good many Sunday newspapers. Second, there is a group which is equally vehement, in opposition. These include the sentimental liberals, who feel that the bearing of feeble-minded children is one of the rights guaranteed the individual by the constitution. The third group is represented by those who make a sincere attempt to find the facts to arrive at some reasonable program.

This effort to find dependable facts carries some persons to the position taken by Dr. Kennedy tonight, for he feels that present data are too difficult to unravel, and that we are therefore not justified in any active steps. This is an attitude which I cannot believe to be sound. We must utilize the facts at present available and act on the conclusions arrived at. There is no way of avoiding some decision. To decide to allow the definitely feeble-minded persons to continue to have children is as much a positive program as to decide to sterilize them. Although we may not be certain, we must go the way which is most probable. This, as a matter of fact, is the way man has always handled his social and political problems.

Let us consider what may be accomplished on the basis of the most dependable facts that we have at our command at the present time. Certain apparently carefully compiled statistics are to me impressive. For example, it has been calculated that one out of every ten of the feeble-minded in this country have come of feeble-minded parents (Punnett, Fisher). That means if all the obviously feeble-minded are sterilized the number of feeble-minded in the next generation will be reduced by 10 per cent. The question to be decided is whether it is worth while to sterilize or segregate, if you will, all the obviously feeble-minded in order to bring about a reduction of the feeble-minded in the next generation of only 10 per cent. Dr. Kennedy thinks that the benefits of such a program are too remote in the future to be worth aiming for; others will feel that the length of time required to produce results is the best reason for an immediate start.

Sterilization of the feeble-minded has, however, an individual as well as a broad genetic aspect. One does not refuse to treat a case of pneumonia because further cases are not thereby prevented. A person with a fair chance of having feeble-minded children must of course be considered also as an individual. If such persons appear to be incapable of taking care of potential children, whether these turn out to be normal or mentally deficient, then sterilization may have an immediate social indication quite aside from the remote genetic one.

MEETING OF JANUARY 12, 1937

The following papers were presented:

Pyeloureteritis in Pregnancy: Etiology, Acute Phase, and Treatment. Dr. Herbert F. Traut. (For original article, see page 392.)

End-Results of Urinary Tract Infections Associated With Pregnancy. Dr. E. Granville Crabtree. (For original article, see page 405.)

OBSTETRICAL SOCIETY OF PHILADELPHIA

MEETING OF JANUARY 7, 1937

The following paper was presented:

Surgical Complications of Pregnancy. Dr. S. A. Cosgrove. (For original article, see page 469.)

CHICAGO GYNECOLOGICAL SOCIETY

MEETING OF OCTOBER 23, 1936

The following paper was presented by invitation:

Pathology of the Cervix. Dr. Walter Schiller. (For original article, see page 430.)

Episacroiliac Lipoma. Dr. Emil Ries. (For original article, see page 490.)

MEETING OF NOVEMBER 20, 1936

The following papers and case report were presented:

Splenomegaly in Pregnancy. Dr. W. B. Serbin. (For original article, see page 486.)

The Effect of the Ovarian Hormones on the Human (Nonpuerperal) Uterus. Drs. Leon Krohn, J. E. Lackner and S. Soskin. (For original article, see page 379.)

Carcinoma of the Cervix During Pregnancy. Dr. W. C. Danforth. (For original article, see page 365.)

MEETING OF JANUARY 15, 1937

The following papers were presented: **Experimental and Clinical Therapy of Vulvovaginal Mycoses.** Dr. H. C. Hesselstine. (For original article, see page 439.)

The Mortality and Complications of 3,129 Supravaginal Hysteromyomectomies. Dr. H. E. Schmitz. (For original article, see page 480.)

The Oral Administration of Paraldehyde for Relief of Pain During Labor. Drs. Edwin J. DeCosta and Ralph A. Reis. (For original article, see page 448.)

BROOKLYN GYNECOLOGICAL SOCIETY

MEETING OF OCTOBER 3, 1936

The following papers were presented:

Medical Aspects of Heart Disease in Pregnancy. Dr. Arthur E. Lamb. (For original article, see page 456.)

Management of the Dystocia Caused by Occiput Posterior Positions. Dr. J. Thornton Wallace.

protuberance of her abdomen the chief-of-clinic asked that special attention be paid to any disproportion. At this time a diagnosis of twins was made and an x-ray examination requested to confirm or disprove the diagnosis. The x-ray plates showed distinctly 3 fetal heads and spines, confirming the diagnosis of multiple pregnancy but showing triplets instead of twins. She had gained 22 pounds in four and one-half months.

On April 1 labor began spontaneously and proceeded so rapidly that at the end of two hours the cervix was completely dilated and the head of the first baby low in the pelvis. The patient was prepared for delivery and after a right paramedian episiotomy the head, which was lying in R.O.T. position, was manually rotated to an R.O.A. and a living female child weighing 3 pounds 11½ ounces was delivered by low forceps. The second head was easily pushed down into the pelvis and a living male child weighing 3 pounds 9½ ounces was delivered by mid-forceps, position was L.O.A. The head of the third child was likewise pushed into the pelvis in R.O.T. position. Following manual rotation to an R.O.A. position a living male child weighing 3 pounds 14¾ ounces was delivered by mid-forceps.

The third stage was uneventful. Inspection of the placenta indicated that the male children were identical twins and the female a separate ovum impregnation. Inspection of the cervix revealed a deep laceration on the right that required six sutures. The episiotomy was repaired in the routine manner. Mother and babies were in good condition one hour postpartum.

The puerperium was characterized by an elevation of temperature, the highest being 102° on the eighth day, and foul lochia. The pulse, however, was not markedly elevated at any time nor was the patient ever very ill. The temperature fell by lysis and on the seventeenth day she was fever free. She was discharged on the twentieth day in good condition.

The babies were given breast milk by gavage for the first few days and then a formula of evaporated milk and dextri-maltose. The latter they were able to take from a bottle. The babies all did well. Baby 1, a girl, discharged on May 8 had gained 1 pound 9 ounces. Baby 2, a boy, discharged on May 12 had gained 1 pound 10½ ounces. Baby 3, a boy, was discharged on May 8 having gained 1 pound 5½ ounces. All three were in a satisfactory condition and are still living and gaining at this date.

MARGARET B. BALLARD, M.D.

104 West Madison Street,
Baltimore, Md.
June 29, 1937.

Society Transactions

NEW YORK OBSTETRICAL SOCIETY

MEETING OF DECEMBER 8, 1936.

The following papers were presented:

A Study of the End-Results of the Treatment of Amenorrhea and Sterility by Radiation of 128 Married Women Over a Period of Ten Years. Dr. Ira I. Kaplan. (By invitation.) (For original article, see page 420.)

Early Diagnosis of Carcinoma of the Cervix. Dr. Walter Schiller. (By invitation.)

Department of Reviews and Abstracts

CONDUCTED BY HUGO EHRENFEST, M.D.

Collective Review

MENSTRUATION AND ITS DISORDERS

A CRITICAL REVIEW OF THE LITERATURE FROM 1933 TO 1936 INCLUSIVE

HUGO EHRENFEST, M.D., ST. LOUIS, MO.

WITHIN the last few years extensive experimental and clinical studies have yielded much interesting and valuable information in regard to the control exerted by the anterior lobe of the pituitary (A.P.) gland on the process of ovulation, in regard to time and causative relations between ovulation and the menstrual flow, the rôle played by endocrine factors in the various disorders of the menstrual function, and finally concerning the efficacy of certain organ extracts in the treatment of such disorders.

A critical review of this voluminous literature, in part not readily accessible to the gynecologist, seems desirable for the purpose of familiarizing him with this literature and thus enabling him to differentiate between actually established facts and many still unproved theories and opinions. The multiplicity of these investigations and reports inevitably has resulted in some confusion of views concerning the factor or factors responsible for the many possible anomalies of the menstrual function and their therapeutic relief.

Deliberately, this survey has been limited to contributions published between the beginning of 1933 and the end of 1936. Even so and in spite of almost complete elimination of merely experimental endocrine studies on animals, it became necessary to quote in the text 394 references cited in the appended bibliography. This can not be surprising in the face of Mengert's¹ assertion that the volume *Sex and Internal Secretion*, edited by Allen, required consideration of 2474 individual papers (monographs and books being excluded) published in 335 different scientific journals. Reviewing the literature published within but two years on the "Interrelationship of Anterior Hypophysis and Ovary," Fluhmann² carefully selected "only information of possible interest to obstetricians and gynecologists," and nevertheless was compelled to quote 246 papers—he states: "Study of this literature leaves one aghast at the extent and complexity of the problem."

Almost the same statement could be made in regard to the literature of the past four years dealing with the problems of menstruation. At the moment it is not even possible to define the word "menstruation" as presently employed in the literature.

MEETING OF DECEMBER 4, 1936

The following case reports and papers were presented:

Ectopic Gestation Following Pomeroy Sterilization. Dr. Martin H. Lutz (By invitation). (For original article, see page 497.)

Angiomatosis Retinae (von Hippel's Disease, Lindau's Disease) Complicated by Pregnancy. Dr. Mervyn V. Armstrong. (For original article, see page 494.)

Management of Pregnancy and Parturitional Hemorrhage. Dr. S. A. Cosgrove. (Published in *The Southern Medical Journal*.)

NEW YORK ACADEMY OF MEDICINE, SECTION ON OBSTETRICS AND GYNECOLOGY

MEETING OF NOVEMBER 24, 1936

Symposium on Sterility

Eugenic Sterilization in Europe. Marie E. Kopp, Ph.D. (For original article, see page 499.)

Sterilization From the Standpoint of the Internist. John Wyckoff, M.D. (For original article, see page 520.)

Sterilization and Eugenics. Foster Kennedy, M.D. (For original article, see page 519.)

Sterilization From the Point of View of the Obstetrician and Gynecologist. B. P. Watson, M.D. (For original article, see page 512.)

Operative Methods of Sterilization in the Female. Eliot Bishop, M.D. (For original article, see page 505.)

Sterilization by Irradiation. Ira Kaplan, M.D. (For original article, see page 507.)

Legal Considerations for the Physician. W. J. McWilliams, Attorney-at-Law. (For original article, see page 516.)

WASHINGTON GYNECOLOGICAL SOCIETY

MEETING OF OCTOBER 24, 1936

The following papers and discussions were presented:

The Function of the Levator Ani Muscle. Dr. James R. Costello.

Breech Presentation: A Critical Analysis of 285 Cases of External Version, Cesarean, the Anesthesia Used, Incidence of Forceps, Use of X-Ray Diagnosis. Drs. W. C. Danforth and C. E. Galloway. (The original article will appear in a later issue.)

MEETING OF DECEMBER 4, 1936

The following papers and discussions were presented:

Endometriosis. Dr. J. Keith Cromer.

Medical Notes from the Soviet. Dr. Richard L. Silvester.

Functional Dysmenorrhea, an Endocrine Problem and Its Treatment. Dr. J. Kotz. (For original article, see page 38, July, 1937, issue.)

of woman will be vitiated by wider use of the term "menstruation" for a menstruation-like uterine flow which is not dependent on ovulation. We are unwilling to agree with Emil Novak's contention that these flows might as well be called menstruations, because this term is in general use in referring to periodical flows in mature women. It seems ludicrous to see, more recently, authors writing of "restoration of menstruation" in castrated women, simply because administration of certain organ extracts was followed by a bloody vaginal discharge. Such a flow, as a rule, is procured only for one time and thus is void even of the characteristic periodicity. Gynecologists will, or should, not accept Allen's⁷ proposal to term as menstruation any flow due to disintegration of the endometrium under hormonal influence, whether natural or artificially produced. Much confusion and misleading ideas would be avoided if, especially in clinical reports, authors would clearly differentiate between menstrual and menstruation-like flows.

II. OVULATION

The following vivid description of ovarian activity has been given by Hartman:⁸ The ovary is never resting. Its cellular turnover is probably the largest of any other organ in the female body except possibly the skin. It seems that about 25,000 eggs through degeneration of primordial follicles are sacrificed within the period of a menstrual cycle, so that one choice egg may survive and mature, and by a fortuitous set of circumstances develop into a baby. The many thousands of follicles which degenerate, nevertheless, prove useful, because they give off internal secretions that minister to certain vegetative functions of the female body: first, to keep healthy and active the female organs for possible pregnancy and lactation; second, to preserve the secondary sex characteristics; and third, to provide the proper hormone balance necessary for the feeling of well being needed for the full enjoyment of life. During the middle of the cycle the ovary seems more active, because among the many degenerating follicles, a single one "gets by" and develops to maturity. . . In women like in many other animals, ovulation is a spontaneous process regulated by the function of the anterior pituitary gland.

It has been known for a long time that endocrine activity of the ovaries, even before the appearance of the first menstrual flow, is responsible for the gradual change of the infantile into the mature type of uterus and for the development of the secondary sex characteristics. It has been assumed, and with more recent investigations the fact has been established, that the appearance of the first and of all subsequent true menstrual hemorrhages depends on a complete ovulation cycle, beginning with the enlargement of a primordial follicle and ending in the formation of a corpus luteum, which represents a specific, periodically new-formed endocrine gland with its own specific hormone or hormones.

Zondek, as the first, established the control of the anterior lobe of the hypophysis over the complete ovulatory cycle. There is considerable supporting evidence for the assumption that specific activity of the anterior pituitary does not begin until the thymus gland is involuted. Continuing their researches along these lines, Fleischmann and Goldhammer⁹ recently reported that they found in the urine of 9 out of 20 infants, between two and eight years of age, a substance which definitely inhibits the estrus of white mice. In view of certain analogies

I. DEFINITION OF "MENSTRUATION"

In the attempt to bring some order into prevailing confusion and inaccuracies of terminology, we shall here use the term "menstruation" to designate the physiologic process which between menarche and menopause periodically prepares woman for the implantation of a fertilized ovum. "Menstrual flow" is the uterine hemorrhage associated with the elimination of the pregravid decidua in case the anticipated impregnation has not taken place.

Outside of these true menstrual flows there can occur, spontaneous or artificially produced, sanguineous discharges from the uterus which must be termed "menstruation-like" flows when occurring in fairly regular intervals. We shall say more about them later.

The old and time-honored conception of "menstruation" as a manifestation of a merely local, uterine process had to be discarded after it had been established that there occur cyclic changes not only in the ovaries but also in the endometrium (Hirschmann and Adler), and after it had become clear that these periodic structural changes in both organs are intimately related to simultaneous systemic changes of the entire organic structure of woman, changes which definitely modify all metabolic activity and even the otherwise almost constant chemie constitution of body fluids. Thus was evolved the generally accepted view of the intimate and purposeful connection between menstruation and pregnancy. An important and essential part of this view necessarily is the conception that there can be no menstrual function without ovulation.

Corner, Hartman, Allen among many others have shown that a periodic, menstruation-like flow without preceding ovulation is a fairly frequent occurrence in normal monkeys, especially during the summer months, and an occasional occurrence also in woman. Anatomists, embryologists, and other scientific investigators thus began to speak of "anovulatory menstruation." Such usage of the term menstruation undeniably is objectionable from the viewpoint of the obstetrician, since it runs counter to the indisputable fact that a true menstrual flow depends upon the formation of a corpus luteum. R. Schroeder (in Veit-Stoeckel's *Handbuch der Gynaekologie*) insists that a menstrual flow definitely represents the uterine hemorrhage which terminates a complete ovulatory cycle and originates from an endometrium in its typical secretory phase of development. All other periodic hemorrhages can be designated only as "menstruation-like."³ With considerable emphasis similar views have been expressed by Robert Meyer, Muehlboeck,⁴ Zondek,⁵ Shaw,⁶ and many others. Shaw refers with slight irony to Novak's "still improved" contention that such anovulatory flows in women are more frequent than generally assumed. The possibility of such an occurrence now has been established, but it seems entirely unjustified, in my opinion, to assign to this phenomenon any particular importance in the problem of sterility. Such flows without preceding ovulation do occur in some monkeys occasionally, but there certainly is no proof that they continue in women for periods so long as to account for a sterility persisting for years. Even women who actually menstruate only two or three times a year are not necessarily or often sterile.

Scientifically the menstrual function has been recognized as a local and general systemic, periodic preparation for impregnation. This great and valuable advance in our information concerning the biology

patients, concludes that menstruation and ovulation are two entirely independent processes. He¹⁶ even denies the necessity of a pregravid endometrium for nidation of a fertilized ovum. In a recent third paper,¹⁷ he summarizes his views to the effect that obviously the ideas of Knaus and Ogino of the existence of a safe period are untenable. Similar views have been expressed by Borras.¹⁸ Kreis¹⁹ defends his idea of an independence of endometrial changes from the ovary.

Older efforts of determining ovulation time by graphing waves in various physiologic functions (Jacobi), of "well-being" (Dickinson), of sex desire (Katharine B. Davis, Tinklepaugh, Stopes, Havelock Ellis, etc.), by studying assumed "isolated coitus," wedding dates or results of artificial insemination are, as Hartman justly asserts, scientifically unacceptable. At least more definite are local symptoms and among them especially the "Mittelschmerz" which not so rarely is accompanied by a light "intermenstrual bleeding." Such recorded observations of Mittelschmerz, with or without bleeding, falling somewhere between the fourteenth and nineteenth days of the cycle (counted from the first day of the flow), in general would seem to support the contention of Knaus and Ogino but do not permit any definite deductions as to ovulation time. In none of these studies, writes Hartman, was the condition of the ovaries checked by palpation or abdominal inspection. We must interpolate here reference to a paper quite recently published. Wharton and Henriksen²⁰ discuss in detail the entire "Mittelschmerz" problem and then present a clinical study of 61 cases of intermenstrual pain, in 30 of which laparotomies were performed for various reasons. Data obtained by them indicate that the Mittelschmerz is synchronous with rupture of the mature graafian follicle.

Exact palpation of the ovaries, of the gradual enlargement of the follicle and formation of the corpus luteum is possible only in monkeys, and such palpatory findings, repeatedly controlled by laparotomy, have in every instance shown that at the time of the intermenstrual bleeding a large follicle or a fresh corpus luteum was present (Hartman). Some data concerning systematic palpation of ovaries in human females have been supplied by Dickinson and others.

Observations of peaks in estrogenic hormone levels in the blood in the midinterval (Frank,²¹ Emge,²² Fluhmann,²³ and others) presumably correspond to the ovulation time and are ascribed to the introduction of larger amounts of follicular hormones with full ripening and rupture of the mature follicle. Kurzrok, Kirkman, and Creelman²⁴ presented a paper in which they claimed that the time of human ovulation is also manifested by the sudden appearance of prolan A in the urine. In the discussion of this paper, Frank stated that he is willing to accept this observation as proving a cyclically increased activity of the anterior pituitary but not as establishing ovulation time. Analyzing the local and general symptoms of ovulation, Simonnet and Brandwein²⁵ stress the observation that the intermenstrual pain is usually observed between the twelfth and sixteenth days of the cycle, the increase of follicular hormone, both in blood and urine, between the eleventh and fifteenth, so that seemingly the maximum of folliculin elimination coincides with follicle rupture.

It seems opportune to mention here a few contributions which refer to the fallacy or, more precisely expressed, the impossibility of estimating the time elapsed since follicular rupture by the size or appearance

with results of previous experiments, they feel justified in concluding that this substance represents thymus hormone. We shall have opportunity later to speak of the rôle played by the active hypophysis also in the artificial production of menstruation-like flows with the administration of certain organ extracts. These latter experiments together with new, relatively simple methods of obtaining endometrial tissue for microscopic study (to be described later) at any phase of the cycle, have greatly advanced our information concerning the definite relations between ovarian and endometrial changes.

Most writers still adhere to the four endometrial phases as first described by Hitschmann and Adler, but Allen⁷ suggests the omission of their "interval stage." He substitutes for it his Stage I: a period of postmenstrual repair and growth of the endometrium—the follicular phase under stimulation of the estrogenic factor. In his Stage II the endometrium changes in two possible ways: (a) *If ovulation occurs*, the glands are transformed with change in the nature of their secretions under stimulation of progesterin from the corpus luteum (with some estrogen substance still present in the woman), but he adds: "This second stage is not necessary for menstruation." (b) *If ovulation fails to occur*, there follows a phase characterized by sustained but waning hyperplastic endometrium under the influence of diminishing concentration of estrogenic hormone. "This type of cycle is normal in monkeys out of breeding season and is an occasional occurrence in adult women and may be a frequent occurrence near the times of puberty and the menopause." Allen's Stage III is that of the menstrual hemorrhage which physiologically represents the terminal event of the cycle.

However interesting or important such a classification of endometrial changes may be to the scientific investigator, its incidental assertion, that these two kinds of flows, though absolutely different in their biologic causation nevertheless are identical, seems unacceptable to the clinician. In the present endeavor to gain a clearer understanding in the complex problem of "functional uterine hemorrhages," the gynecologist will do well to limit the term "menstruation" strictly to the flow resulting from the disintegration of an endometrium variously designated as predecidual, pregravid, progestational, clearly expressing structural preparation for pregnancy. Allen,⁷ Corner,¹⁰ Hisaw, Kaufmann,¹¹⁻¹³ Loeser,¹⁴ Zondek,⁵ and many others, experimentally on animals and more lately on castrated women with the administrations of certain endocrine preparations, have conclusively shown that this phase of the endometrium is due solely to the specific hormone evolved by the corpus luteum.

Before entering into a discussion of clinical differentiation between true menstrual and pseudomenstrual or so-called functional uterine hemorrhages, it will be necessary to deal with newer information concerning the time of ovulation.

III. THE TIME OF OVULATION

Interest in the time of ovulation was greatly stimulated by the wider spread, under sanction of the Catholic church, of the use of the safe period as available means for the prevention of impregnation. From this special viewpoint this question is thoroughly and most interestingly discussed in a small volume by Carl G. Hartman.⁸

By way of introduction, we may refer to the fact that Araya,¹⁵ in contradiction of generally held views, from observations made on 464

carried out in various ways practically agree in the finding that in the overwhelming majority of normally menstruating women ovulation occurs near the middle of the interval.

IV. MENSTRUAL FLOWS

The determination that a given uterine hemorrhage represents a true menstrual flow depends on the proof that it originates from an endometrium in its characteristic secretory phase. As already mentioned, it is not any longer necessary to curet a patient (in a hospital, under anesthesia) for this purpose. Smaller pieces of endometrium, sufficient for microscopic study, are now obtained in the office, without noteworthy discomfort, by various means at any phase of the cycle. Some gynecologists use a very small (monkey) curet (see Sturgis and Meigs³¹). Burch³² designed a suction cannula. A similar cannula is employed by Novak³³ which more recently has been modified by Tamis.³⁴ It may be stated in this connection that these methods are valuable not only for the purpose of scientific investigations but also for clinical purposes, as, e.g., in determining the specific endocrine functional anomaly responsible for various disorders of the menstrual flow. It also must be emphasized that these methods should never replace a thorough curettage in any case in which a uterine malignancy is suspected. For reliable diagnosis complete removal of the entire endometrium is essential. Another shortcoming of studies of small pieces of endometrium is suggested by the claim of Bartelmez³⁵ that there is a definite variability in the histologic picture of the menstruating endometrium in various regions of the uterine cavity. This observation harmonizes with studies made by Markee³⁶ on pieces of endometrium implanted into the eyes of six monkeys. However, Robert Meyer³⁷ is unwilling to accept the claim of Bartelmez that at a given moment the various parts of the endometrium will exhibit different degrees, either of pregravid change or of epithelial exfoliation.

Direct observations of cyclic changes in endometriomas have been reported. In a patient of Chydenius³⁸ a large vaginal metastasis had formed from a primary ovarian endometrioma. Repeated removal of small pieces taken from the metastasis enabled him to ascertain that the endometrial tissue of the growth underwent the typical cyclical changes. Engelhard³⁹ recorded regular discharge of blood at every menstrual period from a pea-sized metastatic endometrioma located in a small labium.

Before entering into a discussion of endometrial structural changes culminating in the menstrual flow, it will be necessary to refer to newer information in regard to the *function of the anterior lobe of the hypophysis*.

Mention already has been made of an analysis by Fluhmann,² published in 1933, of 246 papers on the relation of the hypophysis to the ovaries appearing within the two preceding years. It must be obvious that it would be impossible to review here the literature on this same subject published since then. Therefore, we shall limit ourselves to brief references of those contributions which seem significant in regard to present views on normal and disordered menstrual function and to the treatment of the latter with certain organ extracts.

of the corpus luteum. Emil Novak states that in the study of many thousands of ovaries he has never seen the earliest stage of a corpus, indicative of immediately preceding rupture. "In later stages nobody would venture an estimate of the exact time at which ovulation had occurred." It is Papanicolaou's experience that the exact age of the corpus luteum in women could not be recognized even from detailed histologic study. Hartman, himself, admits only his ability to differentiate between a very young and very old corpus luteum, and asserts that in monkey and human female an estimate of the age of a corpus is bound to lead to gross errors. However, systematic inspection of ovaries of women and monkeys, in general, proves that in the vast majority of instances ovulation falls close to days fourteen to sixteen of the cycle, that is, takes place when the endometrium changes from the late proliferative into the early secretory phase. All this, Hartman admits, does not exclude the possibility that exceptionally ovulation might occur at any other time which, as we should remember, is contrary to Ogino's most emphatic assertion that ovulation takes place only between the eleventh and sixteenth days and to the claim of Knaus that the mature follicle ruptures exactly fourteen days before the ensuing menstrual flow.

Knaus²⁶ developed his method of determining ovulation time in woman on the basis of Reynold's observation that the uterine muscular tonus is increased under estrogen influence and relaxes with the formation of the corpus luteum. In this latter state, Knaus found that the hormone of the posterior pituitary lobe (puitrin) proves ineffective on the uterine muscle. He thus arrived at the conclusion that the endocrine activity of the corpus luteum of menstruation always lasts exactly fourteen days. This claim has never been confirmed by any other investigator. Hermstein,²⁷ studying 30 women by means of the Knaus method (small rubber balloon in uterine cavity connected with a manometer), found at least a few exceptions. Morgan, Moir, Tachezy²⁸ and others disagree with Knaus but some of these discrepancies, as pointed out by Hartman, might possibly be explained by occasional anovulatory (menstruation-like) flows, whose occurrence also Knaus²⁹ admits. Knaus thinks that the nature of such a flow, i.e., the absence of a corpus luteum, can be recognized by a positive uterine response to puitrin within ten days of the next expected flow. A clear and critical analysis of the literature dealing with ovulation time, particularly in its relation to the problem of the safe period, will be found in a paper by Emge.²² Shaw⁶ thinks that a fairly free interval bleeding might be wrongly interpreted as an anovulatory "menstrual" flow, but that, on the other hand, a true menstrual flow at an irregular time may be due to the premature rupture of an almost mature follicle as a result of coitus, a phenomenon which is almost the rule in certain animals.

No control experiments are as yet available in regard to the recent observation of Burr, Hill, and Allen³⁰ that in rabbits the exact moment of the rupture of each follicle can be discovered by a registrable change in electric potentials.

To obviate repetition we shall speak later of attempts to influence ovulation time by the administration of certain hormones.

Concluding this consideration of chronologic relation of ovulation to the appearance of the menstrual flow, we can say that investigations

lating hormone. Approximately in this manner the cyclicity of ovarian and endometrial function is explained on the basis of a cyclicity of anterior pituitary activity.

Only slightly different is Hartman's⁸ description of hypophysis-ovary interrelations. Prolan A stimulates the growth of the follicle, the latter secretes more estrogenic hormone, which affects the uterus, endometrium and vaginal mucosa. Continued output of prolan A combined with prolan B brings about ovulation and formation of a corpus luteum. This starts the secretory phase in the endometrium. Sloughing of the epithelium brings the flow which ends the cycle. Still another slight variation of views can be noticed in the report of experiments made by Brindeau, H. Hinglais, and M. Hinglais.⁴³ They claim that prolan A (Zondek) consists of two components, one stimulating follicle maturation and another sensitizing the follicle to the luteinizing properties of prolan B.

There is, or at least was up to recently, some dissension of opinions concerning the rôle played by the mature and unfertilized ovum both in the formation of the corpus luteum and in the development of the pregravid phase of the endometrium.

Among recent writers, we find Schoeller⁴³ still adhering to Robert Meyer's view that the transition of the proliferative into the secretory stage of the endometrium occurs under the luteinizing effect of the mature ovum. Westman,⁴⁴ on the other hand, feels that most painstakingly performed experimental studies seemingly have supplied convincing proof that the luteinization process is not dependent upon any hormonal influence exerted by the not fertilized ovum. The most important work in this respect has been done by Zondek who in a recent paper⁵ remarks that the idea of a supremacy of the egg cell has been given up ever since he had definitely demonstrated that corpus luteum formation is solely controlled by anterior pituitary function.⁴⁵

Prevailing disagreement concerning the factor or factors which cause the endometrial bleeding at menstruation time, in the main, is due to the insistence on the part of some scientific investigators that true ovulatory menstrual flows and menstruation-like anovulatory flows are identical phenomena. Common to both is the fact that they probably are caused by quantitative changes in certain sexual hormones; they differ, however, in regard to the structural condition of the bleeding endometrium. With but few exceptions modern writers explain the hemorrhage on the basis of increased or decreased output of follicle or corpus luteum hormones, or ascribe it to a disturbed equilibrium thereby caused between them.

As already pointed out, the idea of a supremacy of the unfertilized ovum is untenable. The few writers, previously quoted, who believe in an endometrial cycle quite independent from the ovarian cycle, stand rather isolated. Thus, we can well limit ourselves here to a discussion of views which explain the periodic uterine flow as due to cyclic alterations of folliculin and progesterin output.

Engle and his coworkers⁴⁶ agree that the problem of the actual cause of "menstruation" (this ambiguous term is used by them) is not yet solved. Three theories are current:

I. It is due to cessation of corpus luteum activity, that is, to the withdrawal of progesterin, which represents the more generally accepted theory, "which is applicable only to the complete ovulatory cycle."

Experimental studies of the last decade, states Evans,⁴⁰ have now given adequate grounds for belief in the existence of at least five separate internal secretions of the anterior pituitary lobe. However, we are here solely concerned with the gonadotropic hormones of women discovered almost simultaneously by Zondek and Aschheim, and P. E. Smith. The gonad-stimulating effect of the anterior pituitary on the ovary is definitely established to be due to two hormones: one, the follicle-stimulating hormone which causes the enlargement and development of the primordial to the mature graafian follicle, the other, the luteinizing hormone which is more directly concerned with the formation of the corpus luteum. Both the ripe follicle and the corpus luteum in turn become sources of other specific hormones. Moricard⁴¹ recently reported the effect of removal of an adenomatous hypophysis in a normally menstruating woman. She became amenorrheic and two years later the internal and external genitalia had become markedly atrophic. Her urine then still showed 10 R.U. of folliculin per liter, but, as pointed out by Moricard, this does not imply continued ovarian activity, because this same phenomenon is commonly observed also in castrated women.

In early pregnancy there appear promptly and regularly (Aschheim-Zondek pregnancy test) in the urine substances which, at first and up to recently, were considered to represent typical gonadotropic hormones produced, under the influence of pregnancy, in enormous quantities by the anterior lobe of the hypophysis. More lately two important facts have been revealed: the substances readily extracted from the urine of pregnant women (or mares) are not produced in the pituitary gland and are biologically only similar to but not identical with gonadotropic hormone extracts made from pituitary gland tissue. For evident reasons the latter are obtainable only in limited amounts for experimental purposes, as a rule prepared by the experimenters in their own laboratories. The so-called anterior pituitary preparations on the market, more correctly termed anterior pituitary-like (A.P.L.) substances, for clinical use are manufactured in larger quantities from the urine of pregnant women and more recently extracted from placentas (Collip's emmenin).

In experiments on hypophysectomized animals, the gonadotropic substances of pregnancy urine become effective on the ovaries only in combination with an extract made directly from the anterior pituitary lobe, which Evans for this reason designates as an essential "synergist." Fevold and Hisaw have suggested that this synergist is identical with the follicle-stimulating hormone of the anterior pituitary gland.

Philipp and Huber⁴² have recently summarized all available evidence, to a great part the result of Philipp's own studies, which very strongly suggests that the gonadotropic substances of pregnancy urine really are produced by the placenta. More will be said later on this question.

After this digression we may return to the rôle played by the anterior lobe in the processes of ovulation and menstruation. It would seem, states Allen,⁷ that the follicle-stimulating hormone of the anterior pituitary (prolan A) induces the growth of follicles and secretion of the follicular hormone, which latter reacts on the anterior pituitary to induce secretion of the luteinizing factor (prolan B). The latter aids in the development of corpora lutea which produce the hormone progesterin. The follicular hormone (and possibly also progesterin) may temporarily act on the anterior pituitary, depressing its secretion of follicle-stimu-

curves, 11 showed a peak between eight and eighteen days before onset of next flow. A second increase of estrin levels in the blood is seen in 5 of the curves within four days before or during the flow. In 2 instances occurred only one rise during the three days before flow, and in one case but traces of estrin or negative test were obtained throughout the whole cycle. Slight discrepancies in the findings of this series as compared with those of Frank and others, in the belief of Fluhmann, most probably are explained by a newer, more sensitive test used by him. Smith and Watkins⁵⁰ studied in two normally menstruating women the urinary output of estrogenic and gonadotropic hormones during two and four normal menstrual cycles, respectively. They admit that there is at present no method available to determine exactly the amount of gonadotropic factors in the urine of nonpregnant women. The follicle-stimulating hormone was consistently demonstrable only immediately before the flow, but maximal excretion, regardless of the length of the cycle, in every instance occurred on the twelfth or thirteenth day before onset of flow, almost exactly coinciding with the peak of estrin (folliculin) elimination in the urine.

Allen and coworkers⁵¹ analyzed the urine of five adult chimpanzees for estrogenic content during various stages of the menstrual cycle. They found highest values at the time of genital swelling, the lowest at the time of uterine flow.

A fall of the estrogenic blood level, as previously mentioned (Theory II), is assumed to account for the anovulatory menstruation-like flow. Thus the hypothesis was advanced that also for the true menstrual hemorrhage the seemingly physiologic drop in estrogen and not the appearance of corpus luteum hormone represents the immediate cause for the endometrial bleeding. Strong evidence against any such assumption has been furnished by Kaufmann.^{11, 12} He had previously shown that a typical secretory endometrium can be artificially produced only when the administration of a certain amount of folliculin is followed by a sufficient amount of progestin. He repeated this experiment on a castrated woman but continued with the introduction of large doses of follicular hormone also while giving the corpus luteum hormone. Nevertheless, there occurred one hemorrhage, the removed endometrium exhibiting the characteristic secretory phase. Thus he contradicted Clauberg's argument, that a flow from an artificially stimulated endometrium, in the experiments of Kaufmann and others, might have been due solely to the cessation of administration of the follicular hormone. In another patient Kaufmann injected large amounts of folliculin for several days before and also after removal, during operation, of a corpus luteum. Nevertheless, she began to bleed within two days after operation. In his belief these two experiments strongly support the idea that the true menstrual flow depends upon cessation of corpus luteum influence.

Theory III mentioned by Engle refers to the existence of a specific bleeding factor.

The bleeding, writes Hartman,⁸ occurs "upon the withdrawal of estrin and corpus luteum hormones, when some yet unknown outside factor, probably pituitrin, brings about constriction of the blood vessels and necrosis of endometrial tissue, which is followed by sloughing of

II. It is due to a lowering of the estrin level. This theory is evolved from the finding that in monkeys there exists a nonovulatory cycle (Allen-Corner hypothesis).

III. It is due to direct stimulation of the endometrium by some substance liberated by the anterior hypophysis (a theory first advanced by Hartman, Firor, and Geiling⁴⁷).

Before entering into a critical analysis of these three theories and citing other literature, we will emphasize that for the sake of precision the terms "menstrual function" and "menstrual flow" must be clearly differentiated.

As regards Theory I: Sturgis and Meigs³¹ published most instructive microphotographs showing the changes in the endometrium from the proliferative phase, under estrin influence, into the "postovulatory, presecretory" (Hisaw) as soon as ovulation has occurred and corpus luteum effect begins. Knowledge of the fact that the endometrium, with formation of the corpus luteum, enters into the characteristic predecidual phase and with persistence of a corpus luteum of pregnancy develops into a true decidua, naturally led to the conclusion that involution of the corpus luteum of menstruation, that is, diminished supply of progesterin, causes the disintegration of the predecidual mucosa and thus hemorrhage. This conception of the causation of the menstrual flow is well supported by certain experimental findings, of which more later on, and at least one common clinical observation, I think first reported by Halban many years ago. Removal of the ovary containing the last corpus luteum or deliberate excision of the corpus luteum incident to an abdominal operation almost invariably is followed by a menstruation-like flow within about forty-eight hours, independent of the time elapsed since the last menstrual bleeding.

Theory II applies chiefly to the anovulatory pseudomenstrual flows. From this viewpoint we can understand why Corner¹⁰ does not ascribe to the corpus luteum any rôle in the actual causation of the flow, but finds its useful action limited to putting the uterus into a proper state for the implantation and nutrition of the fertilized ovum.

Kaufmann,^{11, 12} Loeser,¹⁴ Zondek,⁵ Werner and Collier⁴⁸ among many others have convincingly shown that artificially two types of uterine hemorrhage can be produced, the one from an endometrium in the characteristic secretory phase, which always depends upon a definite dose of progesterin (corpus luteum hormone), and the other from a merely hyperplastic endometrium when artificially supplied estrogen influence is more or less suddenly reduced or eliminated.

While there are at present no methods available of assaying the progesterin contents of the circulating blood (Hartman), the opposite holds true for determining the estrogen levels, designed chiefly by Frank and his coworkers. They ascertained⁴⁹ that in the normal adult woman the estrogenic factor in the blood gradually increases to 25 M.U. per liter within one week of the anticipated flow and with its onset (within two to six hours) disappears from the blood. Considerable variations were observed by them in the amounts of estrogen eliminated in the urine with two periods of maximum excretion, the one in the middle of the interval (the theoretical time of follicle rupture) and the other in the week preceding the flow. The menstrual blood always contains large quantities of estrogenic substance. Fluhmann²³ made individual blood estrin curves for 12 normally menstruating girls. Out of 14 such

fact revealed is the marked irregularity, even among 87 nurses who at the beginning of the study felt certain that they were "absolutely regular." As a matter of fact not one of this group menstruated regularly at a twenty-eight-day interval. Scipiadès⁵⁸ used as his material 55 female students of both the philosophic and medical departments of a German university. He can only confirm the findings of others that absolute regular return of the flow is extremely rare. To identical conclusions comes King⁵⁹ analyzing 354 menstrual flows in 37 normal industrial and college women. Fluhmann⁶⁰ reports on a statistical study covering 747 cycles in 76 healthy California girls. He states: It was impossible to find any instance where numerous consecutive cycles were of the same length. It was impossible to group the subjects into twenty-eight, thirty, or twenty-one-day types. No basis was found for the conception that the cycle generally represents a multiple of seven days. Menstrual flows occur at all phases of the moon. A number of current ideas concerning regularity of the menstrual function, he concludes, will have to be reconsidered.

Ogino's graphed data show that only 0.7 per cent of his cases (Japanese women) were absolutely regular, 10 per cent varying from one to three days, 44 per cent up to ten days, while in 56 per cent the variations amounted to eleven days and more (quoted by Fluhmann).

Holt⁶¹ limited his observations to women who asserted that their flows were "as regular as a clock," or "always on the same day of each month." Even with allowance of three days for variations in intervals, the "regular" ones did not approach anywhere the 90 per cent claimed by Knaus. Hardly one could be found to comply with Ogino's demand for 12 consecutive flows in identical intervals. Though not concerned here with the problem of the "safe period," we must refer to a paper by Latz.⁶² In his series he found in 90 per cent variations from two to eight days, but since this method in his opinion is safely applicable as long as the variations between longer and shorter intervals do not exceed ten days, he considers 80 per cent of all women as regularly menstruating.

Richards⁶³ emphasizes that particularly valuable information can be gained by continued and uninterrupted recording of periods of the same woman extending over several years. In this manner can be revealed systematic variations in intervals according to seasons or subsequent to intervening pregnancies. In one of his patients who kept a menstruation calendar, the flows were less frequent in summer and more frequent in late fall. In another instance, flows came in shorter intervals in late spring and in longer intervals in late fall. Mueller⁶⁴ philosophically discusses the evident rhythmicity in various vital processes and the regular variations in the vegetative nervous system. Such variations beyond doubt are caused by seasonal changes and by the twenty-four-hour cycle of the full rotation of the earth around its axis with the alternation of day and night, but also are influenced by the revolving of the moon around the earth in a twenty-eight-day cycle, as is noticeable particularly in animal life.

In the opinion of Guthmann and Oswald⁶⁵ no doubt any longer can be felt concerning a time coordination of rhythmic variations of atmospheric and other extraterrestrial (cosmic) conditions to some of the various biologic processes which are rhythmic. However, it remains difficult to discover the more direct causal connections in regard to the rôle played, e.g., by the sun or possibly by the moon. In popular

the surface layer." He particularly emphasizes that it has been shown that the hypophysis probably is necessary for the action in relation to bleeding.⁵²

Fluhmann⁵³ is willing to acknowledge that Allen's "estrim deprivation theory" offers an acceptable explanation of the bleeding in an anovulatory cycle, but he considers this theory inapplicable to the true menstrual flow, because, in his own studies, he found that it may occur also at a time when the amount of estrogenic substances in the blood is high, and that considerable rise and fall of these substances in the blood is found associated with amenorrhea. These facts induced him to believe that some other factors must also play a part in the origin of the true menstrual flow.

Analyzing "endometrial findings in menstrual disorders," Anspach and Hoffman⁵⁴ met with several confusing facts in regard to the question of a "bleeding factor." There is first the now well-known possibility of a normal menstrual flow coincident with regression of a corpus luteum but also of menstruation-like flow in the absence of a corpus luteum. Second, a corpus luteum may be formed and persist, resulting in an amenorrhea. Third, administration of hormonal products, so far available on the market, has a doubtful influence on the menstrual function of the adult woman. "Thus the conclusion can be scarcely avoided, that there is some factor yet to be found to explain the uterine bleeding. Experiments apparently indicate that anterior pituitary hormones, as well as estrin and progestin, play a part in the bleeding mechanism, but just how, we do not know. It may be due to some positive mechanism thus far unexplained."

Among several other articles dealing with this mooted question, we shall quote but the one recently published by Wilson and Kurzrok.⁵⁵ They agree with the conclusions of Hartman and coworkers that the bleeding per se is due to a special nongonadotropic hormone from the anterior pituitary, and offer the following hypothesis of a bleeding mechanism applicable to all functional or hormonal forms of uterine bleeding, normal and abnormal: There is an anterior pituitary hormone separate and distinct from the follicle-stimulating and luteinizing hormones. It is not gonadotropic but works directly on the endometrium. Its production is stimulated by the follicular hormone. Its activity is inhibited, but not destroyed, by progestin. When a certain concentration of this "bleeding hormone" has been reached, the actual onset of bleeding occurs, providing its action is not fully inhibited by corpus luteum hormones. The bleeding stops with the exhaustion of this hormone. To this hypothesis of Wilson and Kurzrok we must add that Witherspoon and Collins⁵⁶ even speak of the still unknown hormonal factor which controls cessation of the normal menstrual flow.

V. PERIODICITY OF MENSTRUAL FLOW

Extensive statistical investigations in regard to certain aspects of the "safe period" incidentally revealed the noteworthy fact that normal menstrual function is periodic but hardly ever regular. It would be impossible and useless to quote here all the data that have been published in the last few years, and it will be sufficient to show the striking agreement in information supplied from all parts of the world. Edward Allen⁵⁷ gives exact date records furnished by 110 pupil nurses of a training school, covering 1414 menstrual periods. The most noteworthy

Barer and Fowler¹⁰ stress the striking discrepancy among writers in regard to the amount of actual blood loss, which is variously given as from 1 to 20 ounces, or between 20 and 500 gm. Most commonly Hoppe-Seyler's figure of an average of 37 c.c. is accepted. They used, on 100 normally menstruating women, an entirely new method. All blood was carefully collected on cellulocotton pads, and the material analyzed for iron. From the recovered amount of iron was figured the amount of hemoglobin, and from this the blood loss was calculated. Thus they arrived at the following conclusions: The blood loss varies between approximately 6.5 and 178.5 c.c., averaging 50.0 c.c., about one-half of the women losing approximately 23 c.c., and other half 68 c.c. The duration of the flow and the number of pads used convey only a very vague idea of the actual blood loss.

VII. PARTICIPATION OF VAGINA, CERVIX, AND TUBES IN MENSTRUAL CYCLE

A. *Vagina*.—The follicular hormone is primarily a growth hormone, which affects chiefly the female genital tract and the mammary glands. The wall of the vagina of rodents is the best indicator of such experimentally induced growth (Allen⁷) and on this fact is based the Allen-Doisy biologic test for estrogenic substances. Furthermore, the typical involutionary changes in the vagina during menopause as a result of cessation of normal ovarian activity are well known. In view of such evident relationship between vaginal mucosa and ovarian function, it seemed fully justified to assume that this mucosa in some form would participate in the cyclic changes of ovarian activity in the human female. Most writers give credit to Dierks¹¹ as having first, in 1927, established periodic vaginal epithelial changes incident to the menstrual cycle. He removed pieces of vaginal mucosa from about 30 women, and relating their histologic structures to the respective dates of last menstrual flow, he determined that the vaginal mucosa passes through a sequence of histologic alterations within each cycle.

It seems interesting to follow chronologically the variations of views expressed by successive investigators. Adler,¹² the coworker of Hitschmann, in 1928, fully confirmed the findings of Dierks and described the changes as follows: In the first half of the intermenstruum the vaginal epithelium proliferates, the flattened cells increase and cornify. In the premenstrual period a clearly differentiated layer forms in the most superficial part of the cornified zone, which disappears after the flow and is formed anew in the interval. This "functional layer" is particularly marked during pregnancy and is absent during amenorrhoeic periods of prepuberty, climacterium, puerperium, and lactation.

In 1929, Walter¹³ states that definite cyclic changes occur in the vagina of the mouse but not in the human vagina. He agrees that the upper horny layer is cast off but denies that this takes place in any periodic manner. He emphasizes that different portions of the vaginal wall at the same time will show very dissimilar pictures in regard to this layer. He argues that the vaginal lining is not a true mucosa but epidermis, and as such shows in the usual manner casting off of the top horny layer with regeneration from the basal layer.

In the belief of Geist,¹⁴ in 1930, the vaginal mucosa undergoes cyclic changes probably dependent on the ovarian hormone. At the present time, he states, it is difficult definitely to accord each picture its proper place in the cycle. "Naturally certain variations in ovarian and en-

opinion, varied and prompt effects of the lunar phases are often taken for granted, and scientific proof for such an effect in some respects is not entirely wanting. Thus one can easily understand the widespread belief in an intimate relation of the twenty-eight-day moon cycles to the menstrual cycles. Guthmann and Oswald carefully review the extensive literature which gradually has accumulated since Svante Arrhenius first endeavored to establish causal relations between lunar phases and pathologic phenomena in man (a question widely discussed again within the last few years). Studying the histories of 10,393 patients of the Gynecologic Service of the Frankfurt University Clinic, they ascertained that with marked frequency normal or unexpected onset of a menstrual flow occurs either at the time of a full or a new moon. "From a biologic viewpoint such an influence (of the moon) on the menstrual flow is entirely creditable. We know that, in spite of its dependence on spontaneous cyclic variations of endocrine activities, the menstrual cycle also is retarded or accelerated by many external factors and influences, among which we shall have to include a cosmic influence."

In conclusion, we shall mention a hypothesis recently propounded by Theobald.⁶⁶ "There is no rhythmical function of the body, apart from menstruation, which is not accepted as being controlled by a center in the brain." The regularity of the menses is a phenomenon that suggests a central rather than a haphazard hormonal control. On the basis of some clinical observations (that amenorrhea can be caused by mental strain, that the menstrual cycle can be changed by hypnosis or can be stopped by morphine, etc.), he evolves the theory that afferent stimuli to a menstruation center in the hypothalamus are provided by the ovarian hormones and by nervous stimuli from the generative organs and the cerebral cortex, while the efferent stimuli from the center operate through the anterior pituitary gland.

If this hypothesis is correct, he concludes, the correct method of treating menstrual disorders, provided ovaries and anterior pituitary are functioning normally, for the majority of cases is to treat the center directly by suggestion or indirectly by promoting the general well being by dietetic and hygienic measure.

VI. MENSTRUAL BLOOD LOSS

Normal menstrual blood does not coagulate. Most carefully planned studies of Dogliotti⁶⁷ furnish proof that this lack of coagulability is not due to the admixture of follicular or corpus luteum hormones but solely to the absence of both fibrinogen and thrombogen. Also Daniel and Florian⁶⁸ emphasize the difference between normal circulating and menstrual blood, and ascribe lack of coagulability of the latter to deficiency in fibrogen and richness in tryptic ferments. These writers claim to be the first to ascertain that just before and during the menstrual flow also the circulating blood temporarily becomes less coagulable. (We are not aware of any study in regard to possible differences in this respect between ovulatory and anovulatory uterine hemorrhages, though this point might prove of scientific and practical importance.)

Increased loss of blood is due either to a more profuse flow or its undue prolongation. In the opinion of Hirsch-Hoffmann⁶⁹ the latter condition is caused by unusually slow elimination of the menstrual endometrium, which then shows striking variations from the characteristic histologic picture. He ascribes prolonged menstrual flow to some deficiency in the involution of the corpus luteum.

viscosity of the discharge. He feels, however, that the solubility of the cervical mucus varies at different stages of the cycle solely as a result of varying amounts of added secretions from uterine body and tubes. These latter secretions certainly are influenced by follicular hormones, and thus one might have to admit that there actually exists a relation between consistency of the cervical mucus and ovarian activity. As a matter of fact, the rubbery cervical plug during pregnancy has been explained as due to the absence of the solvent action of the combined tubo-uterine secretions.

C. Tubes.—In a paper, published in 1928, Novak and Everett⁸⁴ presented a careful review of the entire literature dealing with cyclic changes in the tubal mucosa. On the basis of extensive studies, they themselves had made, they arrived at the conclusion that, while the tubal mucosa does not normally participate in the bleeding phenomenon of menstruation, its epithelium exhibits definite cyclic changes comparable with those of the endometrium.

However, it seems that in the absence of an endometrium, the tubal mucosa is likely to bleed vicariously. This can be noticed in instances in which after a vaginal hysterectomy, a part of the preserved tube had been caught in the vaginal scar. Strassmann⁸⁵ utilized this capability of the tubal mucosa to bleed under ovarian influence for the purpose of restoring a functioning menstrual channel. We shall have to say more of this operation in a later chapter.

In 1929, Tietze⁸⁶ described in detail cyclic changes observed in 44 tubes removed from regularly menstruating women. Particularly marked are the alterations in the ciliated cells, which show greatest development at the fourteenth and fifteenth days of the cycle, that is, at the time when the ovum is extruded from the ruptured follicle and has to be transported to the uterine cavity. More recently Jaegerroos,⁸⁷ polemizing against a contrary view of Westman, insists that his own investigations definitely establish in the human female the participation of the tubes in the cyclic menstrual changes.

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ometrial cycles with some overlapping and with individual differences suggest that in some patients also in the vagina the same variable condition prevails."

Stieve⁷⁵ feels unable to accept Dierks' theory, because he not only found different pictures in the vaginal mucosa corresponding to the same phase of the menstrual cycle but was able to ascertain that similar structural changes occur also in the epithelial layers of the oral cavity and esophagus, both in men and women.

In 1933, Papanicolaou⁷⁶ definitely determined that the vaginal secretions of the human female change typically in the various phases of the menstrual cycle as he had previously established for certain animals. Rhythmic changes, coordinated with ovarian activity and ovulation, in the vaginal epithelium of a large group of monkeys were described in 1935 by Davis and Hartman.⁷⁷

"Are There Cyclic Changes in the Human Vaginal Mucosa?" is the title of a recent (1936) contribution by Zondek and Friedmann.⁷⁸ Emphatically they answer this question in the negative. There are changes, often found to a varying degree in the same vagina, but they are not cyclic. In some cases of primary amenorrhea, histologic pictures are seen identical with those in women with normal ovarian function. Administration of estrogenic hormones, in the absence of normal ovarian activity, does not change the histologic structure of the vaginal mucosa (however, appearance of cornified squamous cells after administration of estrogenic substances to menopausal or castrated women has been recorded by Papanicolaou and Shorr.⁷⁹) Zondek and Friedmann conclude with the apparently valid argument that recorded differences in the biologic reaction of the vaginal mucosa to cyclic ovarian activity are easily explained by the fact that in different species the vagina itself is embryologically developed in different manners.

Incidentally, we will mention that Fagioli⁸⁰ failed to discover any noteworthy changes in the pH of vaginal secretions in the course of the menstrual cycle, but, of course, he could not make these tests during the flow.

B. Cervix.—Some time ago R. Schroeder and Nuerenberger found that the mucosa of the uterine isthmus participates in the periodic changes of the endometrium, and this view is now rather generally held.

Emil Novak (in Curtis' *Obstetrics and Gynecology*, 1933, W. B. Saunders Co.) asserts that cyclic alterations have never been established for the mucosa of the cervical canal. Wollner⁸¹ describes observations made on strips of cervical mucosa removed from time to time from the same women by means of a Hyams' electrode (cutting current of high frequency). He ascertained that, at least in some women, a definite histologic cycle exists.

As an expression of underlying structural changes has been accepted the observation of a definite thinning of the cervical mucus in the mid-interval, usually interpreted as an additional factor favoring conception at this time. Séguy and Simmonet⁸² used this phenomenon in an attempt to determine the time of ovulation. Assaying the estrogenic contents of the urine and inspecting during laparotomy the ovaries in about one-half of their cases, they were able to ascertain that the previously thick cervical mucus became thinner approximately coincident with the rupture of the mature follicle. Moench,⁸³ repeating Kurzrok's experiments in regard to the penetration of spermatozooids into the cervical secretions, agrees that this ability seems to be dependent on the

All communications concerning the publication of our Transactions should be addressed to Edward Allen, 55 E. Washington Street, Chicago, Ill.

Central Association of Obstetricians and Gynecologists

The Ninth Annual Meeting of the Central Association of Obstetricians and Gynecologists will be held October 14 to 16 at the Hotel Adolphus in Dallas, Texas. The guest speaker will be Dr. C. MacFie Campbell, Professor of Psychiatry at the Harvard Medical School. Dr. Campbell will speak on "Personal and Environmental Factors in Obstetrical and Gynecological Practice." The profession is cordially invited.

For further information apply to the Secretary, Dr. Ralph A. Reis, 104 S. Michigan Ave., Chicago, Ill.

International Congress of Obstetrics and Gynecology

Amsterdam, Holland, May 4 to 8, 1938

Attention is again called to this prospective gathering which promises to be a success from the standpoint of attendance, the Directors having had favorable responses from many sources.

Her Majesty, the Queen of the Netherlands, has graciously agreed to assume the patronage of the Congress.

Three main subjects have been listed for discussion at the stated morning meetings, namely eclampsia, thrombosis and embolism, hormones. The following have been invited to conduct the discussions:

I. Eclampsia.	
Pathogenesis	Dr. E. Klabfen, Vienna.
Treatment	Dr. H. Vignes, Paris, and Prof. B. Stroganoff, Leningrad.
Eclampsia From a Geographical Standpoint of View	Prof. K. DeSnoo, Utrecht, and Prof. R. Remmelts, Batavia.
II. Thrombosis and Embolism.	
Diagnosis and Symptomatology	Prof. E. Alfieri, Milano.
Etiology	Prof. D. Dougal, Manchester.
Prevention and Treatment	Prof. E. Wichmann, Helsinki.
III. Hormones.	
Historical Review	Prof. G. Wagner and Prof. C. Kaufmann, Berlin.
Lectures on latest research	Dr. C. Hartman, Baltimore, and Prof. L. Brouha, Liège.

The afternoon meetings will be devoted to papers on a variety of subjects. Contributions to the program are still acceptable, subject to approval by the Directors.

Professor Dr. A. H. M. J. von Rooy, President
Dr. F. C. van Tongeren, Secretary
University Clinic for Obstetrics and Gynecology
Amsterdam, W., Holland.

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(To be continued.)

Items

American Board of Obstetrics and Gynecology

The next written examination and review of case histories of Group B applicants by the American Board of Obstetrics and Gynecology will be held in various cities in the United States and Canada on Saturday, November 6, 1937.

The next general examination for all candidates (Groups A and B) will be held in San Francisco, Cal., on June 13 and 14, 1938, immediately prior to the American Medical Association meeting.

Application blanks and booklets of information may be obtained from Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh (6), Pennsylvania. Applications for these examinations must be filed in the Secretary's office not later than sixty days prior to the scheduled dates of examination.

The Chicago Gynecological Society

At the 1937 Annual Meeting of the Chicago Gynecological Society the following officers were elected:

George de Tarnowsky, President
David A. Horner, President-Elect
Julius E. Lackner, Vice-President
George H. Gardner, Treasurer
Edward Allen, Secretary
R. A. Lifvendahl, Pathologist
R. M. Grier, Editor

For instance, in 1924, Harris studied 24 cases of eclampsia one year after the attack and found that three patients, or 12.5 per cent, showed definite evidence of "chronic nephritis"; this "nephritis" appeared to be the direct result of the eclampsia, since neither the past history nor the physical examination showed any other etiologic factor. Harris also studied 55 women who had suffered from pre-eclamptic toxemia one year previously and found that the appalling number of 33, or 60 per cent, showed signs of "chronic nephritis." Among this latter group, he was able to show that the length of time the toxemic symptoms persisted was an important determining factor in the occurrence of "permanent renal damage." A few years later Gibberd of England brought forth evidence to show that "chronic nephritis may arise *de novo* as sequela to pregnancy kidney. The frequency with which this permanent damage can be demonstrated in previously healthy women depends largely upon the delicacy of the tests for estimating renal function. The most delicate test is a subsequent pregnancy and where this is available we find permanent renal damage in about 57 per cent. If such advanced changes as persistent albuminuria, cardiac hypertrophy, etc., are taken as evidence of chronic nephritis, we find it in only 14 per cent." In evaluating this report of Gibberd it is important to note that although he made the diagnosis of chronic nephritis in 57 per cent of his cases, only 14 per cent showed albuminuria. In other words, in the vast majority of his cases the diagnosis of chronic nephritis was made on hypertension only. Peekham in a study of 74 eclamptic women has shown that 22 per cent had signs of "chronic nephritis" several months after delivery, while Greenhill, Evans and Strachan, and other authors, have reported similar results in post-eclamptic patients.

If it be true that the toxemias of late pregnancy are frequently followed by a chronic disease entity ordinarily called by obstetricians, chronic nephritis, there must be a process active in the acute toxemias which is carried over to the chronic stage and which is therefore common to both clinical states. To know this common factor with certainty would seem extremely important, not only because of the light such knowledge would throw on the chronic sequelae of the toxemias but also because of its bearing on the nature of the acute toxemias themselves. As we have indicated, it has been assumed that this common factor is renal, the kidney suffering an acute disease process in pre-eclampsia and eclampsia and then manifesting permanent damage afterward. If this assumption is correct it would be only natural to expect these patients with permanent kidney injury to manifest regularly the ordinary signs of chronic nephritis, such as albuminuria, low renal function, and characteristic changes at autopsy. Actually what evidence of kidney damage do these cases show? What is the basic nature of this disease entity, chronic nephritis, as the term is employed by obstetricians?

The clinical characteristics of the condition are plain enough. Hypertension is the predominant finding and sometimes the only one. Albuminuria and abnormalities of the urinary sediment are absent in the majority of cases. The renal function is often normal; edema is minimal or lacking, and the patient has no complaints other than occasional headaches. But the hypertension persists, usually at a fairly constant level.

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THE VASCULAR FACTOR IN THE TOXEMIAS OF LATE PREGNANCY*

NICHOLSON J. EASTMAN, M.D., BALTIMORE, MD.

(From the Department of Obstetrics, The Johns Hopkins University and Hospital)

FOLLOWING the demonstration by Rayer and Lever, almost a hundred years ago, that women suffering from eclampsia excrete albumin in the urine, it was generally believed that the fundamental pathologic lesion in this disease was nephritis with uremia. The frequency with which nineteenth century pathologists found renal changes present at autopsy in women dying from eclampsia accentuated still further the rôle of the kidney in the toxemias of pregnancy. This emphasis on the renal factor in the toxemias has persisted to the present. Such names as "the kidney of pregnancy," "low reserve kidney," and "chronic nephritis in pregnancy" head sections of our most recent textbooks and leave little doubt that the majority of obstetricians, in thinking of the toxemias of late pregnancy, still incriminate the kidney. Consequently, when the late results of the toxemias came to be studied a few years ago and it was found that many preeclamptic and eclamptic mothers were left with permanent hypertension, it was only natural to conclude that these women had suffered some degree of kidney damage from the original preeclamptic or eclamptic attack so that a residuum of chronic nephritis had resulted.

*Read, by invitation, at the Annual Meeting of the Brooklyn Gynecological Society, February 5, 1937.

NOTE: The Editor accepts no responsibility for the views and statements of authors as published in their "Original Communications."

normal six months before death, while in women who succumbed to heart disease and apoplexy, it tended to be normal even a few weeks before the end.

Over 200 blood chemical studies on these 48 hypertensive women showed normal figures with the exception of the specimens taken, during the terminal stages, from the 2 women dying in uremia. Furthermore, if we again except these 2 cases in terminal uremia, the Addis cast count failed to show evidence of nephritis in this series.

The adequate renal function, the normal blood chemistry and the absence of albuminuria and casts which are frequently met in the disease entity under discussion become understandable when we consider the postmortem findings in these cases. In our series of 48 cases just mentioned, there were 5 autopsy studies. In every one of these fatal cases the predominant pathologic lesion was the same, namely, a generalized arteriolosclerosis. The vessel changes in the spleen, the pancreas, and the adrenal were particularly marked, many arterioles showing sclerosis to a degree which resulted in almost complete occlusion. In 2 cases, in which death had been preceded by uremia, the *kidneys* showed similar arteriolosclerotic changes, involving the capillary loops, entering arterioles and even the smaller arteries. However, in the 3 cases in which death was not preceded by uremia, but by cardiac failure (2 cases) and apoplexy (1 case), the kidneys presented minimal changes, the arteriolosclerotic process being concentrated in other organs. Accordingly, it seems reasonable to believe that the degree to which renal function is impaired in this condition depends chiefly on the extent to which the progressive vascular process happens to have involved the kidneys. By the same token, these few cases suggest that the condition we call chronic nephritis in pregnancy is primarily a generalized arteriolosclerosis, in which the kidneys may or may not be concerned.

Medical clinicians have objected for some time to the "chronic nephritis" of the obstetricians, pointing out that in general such cases manifest hypertension only, with no albuminuria, no cast excretion, no red cells in the urine and no diminution of renal function. Herrick, in particular, has stressed the fact that "the loose use of the term, 'nephritis,' in association with the toxemias of late pregnancy should no longer be countenanced." Certainly clearer thinking would result if we employed a term which more nearly connotes the condition we are dealing with, such as "hypertensive vascular disease." Alternative names, but possibly less desirable are "arteriosclerotic Bright's disease," "chronic hypertensive disease," "arteriosclerosis" or "essential hypertension." In those instances in which the sclerosing process has finally affected the arterioles of the kidney with resultant decrease in renal function, the term "nephrosclerosis" of Fahr and Volhard would seem more appropriate than chronic nephritis since the latter phrase implies, of course, an inflammatory origin.

The only other finding which may be noted with any degree of regularity is a narrowing and tortuosity of the retinal vessels, in other words, a retinal arteriolosclerosis. In the event another pregnancy supervenes, the patient shows an aggravation of her hypertension before the seventh month is reached, often during the first half of gestation. The pregnancy may proceed to the expected date of confinement, or, as commonly occurs, the fetus may die in utero and be expelled prematurely. In either event the child is underweight, while the placenta may show an unusual number of infarcts, often red infarcts. Following delivery there may be a slight recession in the blood pressure, but usually it remains indefinitely at a figure only slightly below that observed during pregnancy. Each subsequent pregnancy adds its increment to the hypertension and, as a rule, the exacerbation in the blood pressure occurs earlier and earlier in each succeeding pregnancy. In most of these patients, the hypertension and the retinal arteriolosclerosis persist for years without other findings; some show a more malignant course. Sooner or later, however, one of three clinical pictures emerges. Possibly the largest group of these patients eventually show renal alterations: albuminuria and a rather rapid diminution in kidney function. Once the decreased renal function sets in, the course is a short one and death ensues, often within a few months, from uremia. Another class of these hypertensive women, possibly almost as large as the renal group, later manifest cardiac changes; hypertrophy, occasional attacks of decompensation and finally fatal heart failure. In a third group, characterized usually by a very marked hypertension, death results from apoplexy.

We have just made note of the fact that patients with this chronic nephritis in pregnancy often show normal renal function. Several years ago, Peckham and Stout showed that neither the phenolsulphonphthalein excretion test nor the Mosenthal concentration test is of value in differentiating chronic nephritis in pregnancy from the acute toxemias. During a recent five-year period, A. L. Dippel and I followed, from year to year and from pregnancy to pregnancy, 48 of these hypertensive women at the Johns Hopkins Hospital and studied their renal function from time to time by means of the blood urea clearance test. The average systolic blood pressure of the group investigated was 193.1 mm. Hg, while the average diastolic was 121.9. Most of these patients had been observed for many years, and there can be no doubt that they represented an advanced degree of chronic hypertensive disease. Yet the urea clearance tests of these women, checked by repeated studies at varying intervals, were well within the normal range in over one-third of the group; in only 9 patients, or in less than one-fifth, was it markedly diminished (below 50 per cent of normal). Even in patients who died during the course of the study from uremia, the test was sometimes

But the significance of the vascular factor in the toxemias of pregnancy is not limited to the condition we have just discussed. It is well known that this chronic hypertensive state is frequently initiated by an acute toxemia, the hypertension of preeclampsia or eclampsia persisting indefinitely after the acute manifestations have subsided; indeed, we have already indicated that between a quarter and a half of the acute toxemias of late pregnancy eventually culminate in this chronic hypertensive disorder. Surely, if the one common sequela of preeclampsia and eclampsia is a vascular disease, there must be active in the acute toxemias themselves some very important vascular process. Even a casual survey of recent work supports this suspicion, for the belief is growing that eclampsia with its precursor, preeclampsia, is not a disease of the liver, or of the kidneys, or indeed of any individual organ, but an affection of all the small terminal arterioles (Irving). ✓

This concept was first advanced by Volhard in 1918 and has been accepted by Hynemann, Hinselmann and Fahr in Germany, and in this country by Irving, Mussey, Herriek and others. It is based on evidence obtained from nail folds, ocular fundi, and specimens of muscle taken for biopsy, as well as from autopsy studies on various organs including the kidney, liver, brain, and heart muscle. Hinselmann, Linzencler, Hynemann, Baer and Reis, and others, have noted in preeclampsia changes in the smaller vessels of the nail fold consisting of alterations in the size of the arterioles, with evidence of spasm producing alternate regions of contraction and dilatation, together with elongation of the capillary loops and more or less capillary stasis. Similar capillary changes were found in a large number of eclamptic patients. Several observers, including Mussey of the Mayo Clinic, have studied histologically small sections of muscle taken from preeclamptic patients and have found alterations in the arterioles identical with those which we have just described in the small vessels of the nail fold.

Further evidence that vascular changes play an important rôle in preeclampsia and eclampsia is afforded by the constancy with which spasms of the retinal arterioles are met in these disorders. Mylius, in 1928, demonstrated that in toxemias of pregnancy associated with rise of blood pressure, the primary and most commonly observed lesions of the fundus were spasms and tonic constrictions of the retinal arteries. In the opinion of Wagener also, who has recently made valuable studies in this field, the first visible sign in the retina of preeclamptic patients is a narrowing of the arterioles because of spastic contraction and increased tonus of the walls of the arterioles. This change in the arterioles, he points out, may disappear entirely if there is an early and permanent fall in blood pressure. If, however, the toxemia continues, at some stage of the spastic process permanent sclerotic changes occur in the walls of the arterioles. This is apparently brought about by an ischemia of the vessel walls due to the continual compression of the vasa vasorum by the spastic contractions. The findings of these ophthalmologists indicate, then, that during the acute toxemias of pregnancy, spasms of the arterioles develop which in time cause permanent changes

By whatever name it is called, the conception of this condition as a vascular disease aids materially in understanding the clinical courses which these cases pursue. For instance, why do they usually become worse about the fifth month of pregnancy? The explanation which is ordinarily given for the exacerbation of "chronic nephritis" during pregnancy is that the end-products of fetal metabolism overtax the excretory power of the maternal kidneys. Since, however, the disease usually becomes worse about the fifth month of pregnancy, it is rather difficult to understand how the catabolic products of the fetus, which weighs at this time scarcely more than a pound, could overburden kidneys which had been handling the end-products of, let us say, 140 pounds of tissue. If we are dealing with an arteriosclerotic process, on the other hand, the circumstance becomes quite comprehensible on the basis of the increase in blood volume and cardiac output which gestation entails. Investigators are in general agreement that pregnancy is associated with an increase in total blood volume which approximates 23 per cent and with an increase in the minute output of the heart which averages 50 per cent. These changes throw a considerable burden on the vascular system, and it seems something more than a coincidence, in this connection, that they become marked about the fifth month of pregnancy. Moreover, if pregnancy is such a severe burden on the kidneys as has been supposed, one might expect to find it complicated rather frequently by acute hemorrhagic nephritis. We have recently had occasion to review our cases of acute nephritis in pregnancy and among 16,150 admissions to the obstetric service found 2 such cases, an incidence of 0.02 per cent. This figure is in close keeping with that of Dieckmann who reports an incidence of less than 0.05 per cent in the country at large. In other words, acute nephritis is a rare complication of pregnancy.

If the obstetrician will regard these chronic hypertensive disorders as affections of the vascular system, he will assume a different attitude toward such cases. He will no longer minimize their severity simply because they have no albuminuria, no casts and no diminution of renal function. Indeed, he will scarcely expect these abnormalities in the earlier stages of this disease. He will be inclined, rather, to base his prognosis on the condition of the retinal arterioles and may find it helpful, as we have, to take photographs of the retina from time to time and paste these on the history to serve as a record of the stationary or progressive character of the vascular sclerosis. He will understand that he is dealing with a pathologic arterial tree and will hesitate to impose on these diseased vessels the 50 per cent increase in cardiac output which pregnancy entails. He will not permit the continuance of gestation in clear-cut cases of this disorder and will take appropriate steps to prevent subsequent pregnancies. And, in so doing, he will serve the best interests of his patients.

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DISCUSSION

DR. HERBERT F. TRAUT.—I think those of us who see large numbers of toxemic patients are impressed with the fact that they all suffer from elevated blood pressure to begin with, and that it is a long time after the evidences of hypertension are manifest that one sees anything like a chronic nephritis, as we understand the term. Certainly, from the point of view of demonstrable diminution of kidney function or of retained nitrogenous products in the blood stream, the above statement holds true.

James Young, who for many years studied these conditions in pregnancy, also explained them on a vascular basis. He assigned to most of the acute toxemias of pregnancy a basis of excessive permeability of the vessel wall. He felt in particular that the toxic type of premature separation of the placenta with the excessive blood loss into the musculature, the edema associated with the condition, etc., could only be explained by a tremendous vascular change.

More recently, Page, at the Rockefeller Institute, has studied essential hypertension and chronic nephritis in great detail and has been able to demonstrate that not only in pregnancy, but in essential hypertension in individuals not pregnant, there is a pressor substance which brings about spasm of the arterioles and which eventually, if long continued, produces changes in the vessel wall. Page and Heuer have also demonstrated in human beings that by depriving the kidney of its autonomic nerve supply, they could, in a large percentage of instances, cause a disappearance of the hypertensive syndrome.

What the origin of this pressor substance is, whether it is the same in the non-pregnant as in the pregnant person, is still a matter for guesswork. The old conception of transportation of the villi and split protein products is not necessarily to be discarded. Perhaps we can find a better explanation on the basis of more recent hormone discoveries.

DR. ALFRED C. BECK.—We have been trying to reconcile clinical with pathologic findings and with the medical man's ideas ever since the original work of Vollhardt and Fahr. I hope that this new conception which is being accepted more and more is going to clear up the entire subject of the toxemias. Instead of considering the different entities from the old-time pathologic aspect, we may now consider them as acute or chronic manifestations of a vascular condition.

Many today accept the conception which Eastman has outlined. There are many more pieces of evidence which point in this direction as, for instance, the changes in the spleen, the changes in the adrenals, and the picture in the brain. All of the findings that we observe in eclampsia and in the so-called nephritic cases can be explained on this basis. We have taken a very large step forward. There remains to be discovered what produces these arteriolar spasms.

DR. JOSHUA RONSHEIM.—I should like to ask Dr. Eastman if he will tell us something about how, with the conception he has outlined of the nature of the disease, he now treats these patients.

in the walls of the small vessels. Their observations afford some basis for the fact that eclampsia and preeclampsia are frequently followed by chronic hypertensive vascular disease and indicate that the common factor which links the acute toxemias with their chronic sequelae is not the kidney, but the vascular system.

The autopsy evidence that the arterial tree exhibits profound changes in eclampsia is too numerous to permit more than cursory review. Some ten years ago Jaffé reported that in cases of death from eclampsia the cerebral vessels show extensive changes, varying from slight swelling and poor staining nuclei to an actual hyalinization of the vessel wall with disappearance of the nuclei. It is his opinion that the media is first involved, later the intima, and he is in agreement with Hinselmann in concluding that the injury to the vessel walls is due to spasm of the arterioles which results finally in necrosis of the smaller branches. In the opinion of Domagk, endothelial changes in the vessels play a major rôle in eclampsia and are responsible, directly or indirectly, for a great part of the clinical picture; pulmonary edema, so frequently met in eclampsia, is particularly mentioned as being due to previous capillary injury; the well-known liver changes are interpreted in the same light. More recently Braummühl has described in the brains of women dying from eclampsia an ischemic cell disease which he believes due to vasoconstriction. Benoit and de Friest also attribute the vessel changes in eclampsia to primary spasm of the arterioles.

But it may be objected that some of the most characteristic phenomena of eclampsia seem very directly associated with the kidney, namely: albuminuria, oliguria, hematuria, and cast excretion. As Irving has recently emphasized, vascular spasm resembles in its results very closely the experimental clamping of a vessel; and it is well known that the experimental clamping of the renal artery produces immediate and marked albuminuria as soon as the constriction is released. The sudden onset of marked albuminuria which so often precedes or accompanies an eclamptic attack is thus satisfactorily explained on the basis of an abrupt arteriolar spasm. With massive albuminuria present, casts would be expected since the latter represent merely the tubular solidification of albuminous material in the absence of sufficient fluid to hold the albumin in solution. Oliguria may likewise be accounted for on the basis of arterial spasm since the more severe the spasm the less is the amount of urine which passes through the glomeruli. Hematuria is readily explained by hemorrhage into Bowman's capsule when the spasm of the afferent arterioles is suddenly released.

In reviewing the evidence which points to the vascular system as the common and dominant factor throughout the toxemias of late pregnancy, care has been taken to avoid the question: what causes the arteriolar spasm? In the answer to this query, possibly, lies the long-sought, primary cause of eclampsia an enigma which remains unsolved.

under the demands of pregnancy and labor and to express the variations of cardiac function throughout the pregnancy.

Functional capacity is considered as the expression of the effect upon the circulation of the cardiac structural disease corrected and modified by nature's compensatory ability. It attempts to express more exactly the old idea of compensation without the old anatomic concepts of hypertrophy and dilatation which were included in this idea.

This functional classification has four main categories: Class 1, patients with organic heart disease who are able to carry on ordinary physical activity without discomfort; Class 2a, patients with organic heart disease unable to carry on ordinary physical activity without discomfort, and whose activity is slightly limited; Class 2b, patients unable to carry on ordinary physical activity without discomfort, and whose activity is greatly limited; Class 3, patients with organic heart disease with symptoms or signs of heart failure when at rest, unable to carry on any physical activity without discomfort.

If difficulty is experienced in assigning the patient to a proper functional group, the performance of a test exercise in the physician's presence will often be of great aid. The exact type of the test exercise is unimportant except that it must be one with the use of which the examiner is familiar. He must know the normal reaction to this test exercise, that is, the degree of dyspnea and tachycardia usually evoked in a normal woman, and their duration. Having used dumbbell swinging in the earlier years of this work it has seemed best to change to a stepping exercise. In stepping on and off a 10-inch step at the rate of 20 steps per minute there is less variation in the effort expended by different individuals than in the case of dumbbell exercises to which some adapt themselves more readily than others. The examiner must distinguish between fatigue, which need not be of cardiac origin, and dyspnea, which has a cardiac origin, as reasons for stopping the exercise. Twenty-five steps should be required of a patient thought to be Class 1 or Class 2a. After this exercise the Class 1 patient will show slight dyspnea and tachycardia for about a minute and the Class 2a patient will show moderate dyspnea and tachycardia lasting for more than a minute. A Class 2b patient having to perform this exercise may stop before its completion because of fatigue or dyspnea and will then show moderate or marked dyspnea and tachycardia, or, if she has continued for 25 steps, dyspnea and tachycardia will be marked and will continue well over a minute. It does not seem possible to have a more mathematical rating than the above because of the variable tendency to dyspnea as shown by different types of valvular disease. With mitral disease the tendency is to the production of rapid, shallow breathing and tachycardia, while with aortic disease the tendency is to less rapid and deeper breathing with less tachycardia.

DR. EASTMAN (closing).—In bringing this conception of the toxemias of pregnancy before you I am not deluding myself into thinking that I am presenting new material. However, you will recall that during the past year and a half some five new textbooks on obstetrics have appeared in this country, and in all but one of them the terms "chronic nephritis," "kidney of pregnancy," and "low reserve kidney" receive the usual emphasis. These are the textbooks we recommend to our students and distribute to practitioners throughout the country. Surely, such a nomenclature as this is not one to give these groups a clear conception of the real processes which underlie the toxemias.

In reply to Dr. Ronsheim's question, I am frequently vexed about the correct treatment of preeclampsia. We see every year, unfortunately, a patient or two of preeclampsia develop convulsions while under treatment on our wards. With rest in bed and a low salt diet, many preeclamptic patients improve and do not require termination of the pregnancy. However, in a substantial group the puffy face, the massive albuminuria, and the sudden rise in blood pressure do not yield to treatment and interference with the pregnancy becomes imperative. If the patient is a primigravida, as is usual, and two or more weeks from her expected date of confinement, cesarean section is often the operation of choice in these fulminating cases. In others, which are less fulminating, labor may be induced either by puncture of the membranes or by bougies. The pressing question in this group of cases is of course: when shall we interfere? The correct answer to this question often calls for the greatest clinical acumen and in our hands at least, mistakes are not infrequent.

THE CARDIAC FUNCTIONAL CAPACITY AS AN AID TO PROGNOSIS DURING PREGNANCY*

HAROLD E. B. PARDEE, M.D., NEW YORK, N. Y.

(From the Woman's Hospital, the cardiac clinic of the Polyclinic Hospital and the Department of Medicine, Cornell University Medical College)

IN ATTEMPTING to discuss the subject of pregnancy as a complication of heart disease, one finds that two different viewpoints have been held. The earlier might be called anatomic and concerns itself with the type of valvular lesion, the degree of cardiac enlargement and such evidences of visceral congestion as enlarged liver, pulmonary râles, and edema. The more recent knowledge of the physiology of the circulation and of evidences of cardiac insufficiency has led to what might be called the functional viewpoint. This attempts to measure the efficiency of the circulatory function of the heart and to use this measure as an aid to prognosis and treatment. The anatomic background is practically disregarded.

The classification of cardiac functional capacity introduced by the New York Heart Association¹ has been used for this purpose, in grouping pregnant women with heart disease.² It seems to enable us to appraise, with fair success, the possibility of severe failure developing

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livered at the Woman's Hospital; and were again seen after delivery at the cardiac clinic. Only those diagnosed as having organic cardiac disease were studied, patients with arrhythmia or murmurs of nonorganic origin being disregarded after having been so diagnosed. Fifty-two deliveries of 48 patients with organic cardiac disease were encountered in a service including 3,270 deliveries. This is an incidence of cardiac disease of 1.6 per cent. Eighteen of these deliveries were in primiparas and 34 in multiparas. The diagnosis, both organic and functional, is shown in Table I. It is noteworthy that there are no Class 3 patients in this series which means that no patients in this category applied for admission to the hospital. All came to the clinic in less severe grades of cardiac insufficiency, probably a result of the rather better-than-average education of the clinic patients attending this hospital. They would be less liable to await the last stages of heart failure before applying for treatment.

It is interesting, too, that the Class 1 group is smaller than in the Lying-In Hospital series formerly reported² and the 2a group proportionately larger. The 2b group is of about the same size. An explanation of this different distribution of the patients in the functional groups seems difficult though the fact that cases with mitral insufficiency alone comprised 26 per cent of the earlier series and only 18 per cent of this one, may be significant. It is possible that a number of cases with apex systolic murmurs and no limitation of functional capacity were included in the earlier series and excluded from the later one.

It seems advisable to follow in some detail the course of the illness of those who died, because it is so important for us to understand the relation between their death and their cardiac disease.

Only one of these patients died before leaving the hospital. This was a primipara with mitral stenosis and insufficiency rated as Class 1 functional capacity a week before delivery. She entered the hospital after four hours of labor and was described by the resident physician as "well compensated" at that time. She was six hours longer in the first stage and then two and one-fourth hours in the second stage with a persistent occiput posterior. Forceps rotation and delivery followed promptly, the patient then appearing cyanotic with rapid pulse but no marked respiratory distress; one and three-fourths hours after delivery there was a sudden attack of marked dyspnea with pulmonary congestion and cough and she died in ten minutes. Autopsy revealed findings indicating pulmonary embolism.

Three other women died of heart disease two or three months after leaving the hospital. One thirty-two years of age, a para iii, with mitral stenosis and insufficiency and aortic insufficiency was classed as 2a when first seen in the sixth month; she continued as 2a; she was delivered after one hour first stage and seven minutes second stage. At the time of labor she developed auricular fibrillation which gave place to normal rhythm on the third day. Pulse and respiration remained above normal for a week. She left on the twenty-fifth day after delivery in Class 2b and was under the care of her own physician. She died three months later. The second, thirty-three years of age, para iv, with mitral stenosis and aortic insufficiency, and an electrocardiogram with a coronary T in Lead I, was

It must be emphasized that the classification does not depend upon an estimation of the degree of valvular stenosis or insufficiency or of cardiac enlargement. The physician should not consider the extent of these factors in arriving at the diagnosis of functional capacity. He should confine himself solely to a consideration of what physical exercise the patient states that she is able to perform before developing shortness of breath or palpitation. In addition to this he should observe the patient during and after a test exercise to determine the objective dyspnea and tachycardia resulting. He must compare this history and the observed reaction to exercise with what would be expected of a woman *at the same stage of pregnancy* and with a *normal heart*. He must free his mind of any ideas that "the patient has a severe lesion and therefore her functional capacity must be reduced," or conversely that "she has only a slight lesion and therefore her functional capacity will be good." These are the errors which are likely to be made by those unaccustomed to the method, and it is felt that such errors explain the dissatisfaction which has been expressed with the use of this classification in pregnancy.^{3, 4}

The cardiac burden resulting from pregnancy increases as the basal metabolism of the mother increases, as her weight increases and as the uterine tumor increases. For these reasons the burden increases more sharply after the sixth month than before this time, thus indicating a reason for Carr and Hamilton³ having found 60 per cent of their 63 cases of "heart failure" occurring during the sixth, seventh, and eighth months and only 25 per cent before this and 15 per cent after. The physical strain of labor itself is an important factor if the labor be prolonged and particularly if prolonged in the second stage. An ability to predict the ease of the second stage of labor would be a great boon to one attempting the prognosis of the pregnant woman with heart disease. In spite of this difficulty only 8 per cent of Carr and Hamilton's cases of "heart failure" developed during or after labor. One thing must be emphasized regarding these statistics of heart failure: the term is used by these authors with a much broader concept than is often applied to it. It includes the Classes 2a, 2b, and 3 of the Heart Association categories and so fails to indicate how many of these women were slightly affected and how many were seriously ill with their failure. It is just because the Heart Association classification affords a method of indicating the degree of cardiac insufficiency that it seems to deserve an important place in the diagnosis of the cardiac state of a pregnant woman.

In view of the doubt cast upon this method by Lamb⁴ and by Hamilton,³ it seems worth while to report another series of cases in which it has been used as a basis for prognosis. These patients were from the prenatal clinic of the Woman's Hospital; were referred to the cardiac clinic of the Polyclinic Hospital for prenatal cardiac care; were de-

feel that the death from coronary thrombosis four months after delivery was aggravated by the pregnancy nor the death from bacterial endocarditis.

It is interesting to follow the histories of the patients according to their functional grouping. Of 28 Class 1 patients, one died of pulmonary emboli after forceps rotation of a persistent occiput posterior. One developed paroxysmal tachycardia after placental expulsion which lasted, however, for only fifteen minutes; one became Class 2a during the ninth month and labor was induced at term without evidence of cardiac strain. Two were delivered by cesarean section, one because of a previous hysterotomy, and another because of flat pelvis and non-engagement of the fetal head. Neither of these patients developed unusual dyspnea or tachycardia nor did any of the remaining twenty-three patients in Class 1.

Of 21 patients in Class 2a when first seen, one developed transient auricular fibrillation and died as has been described, three months after delivery; one became 2b in the ninth month and after twenty-four hours in the first stage without progress was delivered by version with no unusual dyspnea or tachycardia. She made an uneventful recovery. One became 2b in the sixth month and was delivered by cesarean section at that time, making a good recovery. One became 2b at the eighth month and was delivered by cesarean section at term with good recovery. She had a pulmonary embolism on the fourth day postoperative but recovered and left the hospital in good condition three weeks after delivery. She was well five months later. One became 2b in the ninth month but was delivered normally after six hours in the first stage and forty minutes in the second. During labor, however, her pulse was about 110 and her respirations were over 25 for the last three hours of the first stage. This, to my mind, indicated a dangerous state of cardiac strain which should not have been allowed to continue for so long a time.

One had an uneventful twin delivery. One was delivered by cesarean section because of flat pelvis and nonengagement of the head. These last two and all of the fifteen other patients in Class 2a when first seen, passed through pregnancy and were delivered without a disturbing degree of tachycardia or dyspnea.

Of the three in Class 2b two have been already described, one dying of bacterial endocarditis two months after delivery and the other of coronary thrombosis four months after delivery. The third was first seen in the ninth month as Class 2b, was delivered by cesarean section and left three weeks later in good condition; a month later in the clinic she was rated as 2a.

It will be seen that delivery by cesarean section was the method of choice for those in Class 2b. For this indication there were four such

classed as 2b when first seen in the fifth month of pregnancy; under treatment with digitalis she continued to be rated as 2b and at term was delivered by cesarean section, had an uneventful recovery and left the hospital on the fifteenth day. Seen in the clinic four months later she was considered Class 1. Three weeks after this she developed an attack of precordial pain and dyspnea, entered New York Hospital and died of coronary thrombosis. The third woman, twenty-nine years of age, para i, was first seen in the eighth month. She was found to have aortic insufficiency and mitral insufficiency and a marked anemia due to bacterial endocarditis. She was classed as 2b; one month later she entered the hospital and was delivered after sixteen hours in the first stage and one-half hour in the second stage without any unusual dyspnea or tachycardia; she was discovered to have a fever on the day after delivery and a blood culture showed a long chain non-hemolytic streptococcus. She died two months after delivery.

Only the first of these deaths could be attributable to cardiac disease aggravated by pregnancy, and this patient was an advanced case who had a history of dyspnea and edema seven years previously during a former pregnancy. It is possible that without this last pregnancy her life might have been prolonged for a number of years. One cannot

TABLE I

FUNCTIONAL CLASSIFICATION	1	2-a	2-b	TOTALS
Mitral insufficiency	8 c c f 2F	1		9
Mitral stenosis	5 b 2F	5 a n 3F		10
Mitral stenosis and insufficiency	14 d g 9F	9 e (mX) 3F	1 (oX)	24
Aortic insufficiency, mitral stenosis and insufficiency		1 l		1
Aortic insufficiency and mitral stenosis		2 (kX) 1F	1 iX	3
Aortic and mitral insufficiency	1	1	1 h	3
Congenital anomaly		2 1F		2
Totals	28	21	3	

Numbers on the upper line opposite each diagnosis indicate the number of cases in the category.

Letters on the lower line opposite each diagnosis indicate the cardiac complications occurring in those patients whose course was other than uneventful.

- a, Became 2b in ninth month; delivered by version on account of no progress.
- b, Became 2a in ninth month; labor induced at term.
- c, Delivered by cesarean because of previous cesarean section.
- d, Persistent oeciput posterior; died.
- e, Delivered by cesarean because of nonengagement of head.
- f, Paroxysmal tachycardia for 15 minutes after placental expulsion.
- g, Prolonged A-V conduction time also present.
- h, Bacterial endocarditis; died two months later.
- i, Became Class 3 in ninth month; improved under treatment; delivered by cesarean. Good recovery. Died 4 months later of coronary thrombosis.
- k, Became 2b at eighth month. Delivered by cesarean section.
- l, Auricular fibrillation developed during labor; lasted two days; left hospital 2b; died 3 months later.
- m, 2a at sixth month; 2b at 6½ months.
- n, 2a at fifth month; 2b at eighth month; uneventful delivery.
- o, 2b at ninth month; uneventful cesarean section.
- X, Therapeutic cesarean because of Class 2b cardiac function.
- 2F, 3F etc. indicate the number of cases in each bracket who were subjected to the prophylactic low forceps.

tion the degree of progress of the labor at this time. When the pulse exceeds 110 and the respirations exceed 24 per minute, I believe that there is a serious degree of cardiac strain.

DISCUSSION

In summary of the results of using the Heart Association rating of cardiac functional capacity in this group of pregnant women it can be stated that there were no cardiac deaths during pregnancy or labor. One woman classed as 2a developed transient auricular fibrillation during labor, recovered from this, but left the hospital as Class 2b and died three months later. Two other delayed cardiac deaths, one from bacterial endocarditis and one from coronary thrombosis, did not seem to owe an aggravation to the pregnancy.

None of the 28 patients rated as Class 1 showed serious cardiac symptoms or signs though two showed slight evidence of cardiac strain. Of the 21 in Class 2a when first seen, one died a delayed cardiac death. Four others became 2b during the sixth, eighth or ninth month but were successfully delivered, three of them at term. All made good recoveries. The remaining 16 remained in Class 2a throughout pregnancy and were delivered without evidence of serious cardiac strain.

Of the three in Class 2b, there were two delayed deaths, not apparently as a result of pregnancy, one patient having been delivered uneventfully by cesarean section at term and dying of coronary thrombosis four months later, the other being delivered spontaneously at term without signs of serious cardiac strain and dying of bacterial endocarditis three months later. The third was delivered at term by cesarean section and made an uneventful recovery.

It seems from the above that it is fair to repeat the statements made in 1929,² about the use of this classification of pregnant patients with organic cardiac disease: "A Class 1 patient will not be expected to give trouble from cardiac insufficiency. A Class 2a patient will probably not give trouble. There is a fair chance that a Class 2b patient will do so." It must be remembered in this connection that if a patient first rated as 2a should later become Class 2b she by this change acquires the prognosis of the more serious group and should be treated accordingly.

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operations and one induced labor at term. Four of the 21 patients in Class 2a became 2b before delivery; only one of the Class 1 patients became 2a before labor.

The application of prophylactic low forceps was a frequent procedure in these cases and was often accompanied by episiotomy. Low forceps were used in 42 per cent of the Class 1 and 33 per cent of the Class 2a patients. This has little to do with the cardiac status of these patients, however, as it is a common practice in this service where 47 per cent of 741 patients delivered during the year 1932 had this prophylactic use of low forceps. It may, however, have had its influence in easing the cardiac strain of the second stage. Seven cesarean sections were performed, four because of cardiac insufficiency.

There is one feature of the cardiac diagnosis which has not appeared in this group but which is of such importance in the prognosis that I feel it should be mentioned. This is the presence of continuous auricular fibrillation associated with valvular or other form of heart disease.³⁻⁵ Owing to the usual tendency to rapid heart rate with exercise in these patients, they need special supervision of their digitalis dosage, so that the heart rate is maintained below 75 when the patient is at rest. Even with this digitalis therapy the heart rate will be more rapid during labor than in a case with normal rhythm. There is in these patients a special danger from the formation of clots in the auricular appendices of these rapidly beating hearts with later embolism of the pulmonary or systemic arteries. This danger is in proportion to the rapidity of the heart rate with effort and to the degree of cardiac insufficiency. A fair rule for the management of these patients during pregnancy is that they should be treated as though belonging to the category next more severe than their functional capacity rating, that is, a Class 1 patient should be managed as if she were in Class 2a and one in Class 2a should be managed as if in Class 2b. I feel that it would be a very rare patient with auricular fibrillation that should be allowed a trial at labor, cesarean section being the method of choice for delivery in almost every case. An exception might be found in a Class 1 multipara who maintained a heart rate of 70 at rest and after the test exercise did not have a count of over 19 in the first ten seconds following.

A word should also be said about the observation of the circulatory function during labor itself. It is not yet possible to offer statistics on this subject but it has been customary to record the pulse and respiration every twenty minutes during labor. The pulse in normal women may occasionally become rapid but the respiratory rate does not rise with it. In certain cardiac patients in the 2a and 2b categories, pulse and respiration rise together. It is my belief that this is an indication of cardiac strain which precedes the appearance of pulmonary râles. It is a danger sign which should lead to prompt termination of the labor by the most available obstetric measures, taking into considera-

sible during the period of antenatal observation or even sometimes at the time of discharge from the hospital. An abundance of evidence has been clearly presented in numerous contributions on this subject that have emphasized this important observation. Accordingly, it at once becomes evident that in order to classify these diseases accurately it is necessary to have frequent observations during the months before and not infrequently during the years following the termination of pregnancy. Only with such data can we more or less definitely and permanently classify our patients. Accordingly, all attempts at classification, at the usual time of discharge from the hospital, must be made subject to correction at a later date. However, for practical purposes experience has taught us that with reservations it is possible in instances of hypertension and the toxemias to classify the majority of our patients at the time of discharge from the hospital. The classification that we employ is not ideal, but we feel that it is the best that has been devised up to the present time, namely, that proposed by Stander and Peckham¹ in 1926. Under this scheme the toxemias associated with hypertension are divided into five main groups: Group I, low reserve kidney; Group II, preeclampsia; Group III, eclampsia; Group IV, chronic nephritis; Group V, unclassified. A modification suggested by Peckham and Stout in 1936² has influenced our diagnoses somewhat during the past year and is, we feel, a distinct advance in the classification. It decreases the number of patients classified as "low reserve kidney" and further increases the group of "unclassified" patients.

TABLE I. INCIDENCE OF "TOXEMIA OF PREGNANCY" ASSOCIATED WITH HYPERTENSION INCLUDING CHRONIC NEPHRITIS

	LOW RESERVE KIDNEY	PRE- ECLAMPSIA	ECLAMPSIA	CHRONIC NEPHRITIS	UNCLASSI- FIED
Full-term deliveries	684	115	18	133	221
Premature deliveries	24	17	4	22	10
Abortions	2	4	4	39	2
	710	136	26	194	233
Total: 1299 cases. Incidence: 11.47%.					

Table I illustrates that there was a total incidence of 11.47 per cent of these various conditions, in a total of 11,336 pregnant women seen in the New York Lying-In Hospital during the period from Sept. 1, 1932, to Sept. 30, 1936, the diagnosis being made at the time of discharge from the Hospital. This incidence is comparable to that given by Peckham³ who has estimated the incidence in the registered patients of the In- and Out-Patient Service of the Johns Hopkins Hospital of Baltimore, to be 13.51 per cent. The importance of classification is brought into the foreground when we realize that ordinarily there is no maternal or fetal mortality associated with the "low reserve kidney" group, and this disease constitutes 54.6 per cent of all our toxemias

HYPERTENSION, NEPHRITIS, AND THE TOXEMIAS OF PREGNANCY*

R. GORDON DOUGLAS, M.D., NEW YORK, N. Y.

(From the Department of Obstetrics and Gynecology, New York Hospital and Cornell Medical College)

THE important rôle played by the toxemias of pregnancy and nephritis in the causation of maternal mortality has long been known. In fact, according to statistics released by the Bureau of Census, Division of Vital Statistics, maternal deaths due to "puerperal albuminuria and convulsions" constituted 25.3 per cent of all maternal deaths in the year 1929, an average year during the period from 1915 to 1932. The figure in the latter year was 20.3 per cent which was the lowest during the entire period of consideration. In addition to this mortality as will be pointed out subsequently, there is an added mortality less tangible and more difficult of estimation. The deaths in this latter group occur during the months or years following delivery and might be divided into two groups: First, deaths in individuals with definite evidence of chronic cardiorenal vascular disease prior to the onset of pregnancy whose expectancy of life is shortened by the pregnancy, and second, deaths in those individuals where the first symptoms of the disease appeared following pregnancy. In this latter group, the concept that pregnancy itself was responsible for initiating the disease process is introduced.

It is possible in the following paragraphs to discuss only a few of the more important facts concerning such a formidable subject as hypertension, chronic nephritis and the toxemias of pregnancy. Unfortunately, for purposes of classification the vast majority of the toxemias of pregnancy are associated with an hypertension, and it is only this group of diseases that I propose to discuss. Accordingly, the toxemia of pregnancy occurring during the first trimester which has the common symptoms of nausea and vomiting, will not be considered. Other more or less vague forms of toxemias occurring in the second and third trimesters of pregnancy not associated with hypertension are also excluded. No discussion of patients suffering from acute yellow atrophy of the liver, will be entered into.

The problem could be greatly simplified if it were possible to separate patients definitely into the three general categories included in the title, namely, hypertension, chronic nephritis, and the toxemias of pregnancy. Unfortunately, however, this is frequently difficult or impos-

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We regard this condition, both the preeclamptic and eclamptic forms, as a single clinical entity not associated with the other toxemias of pregnancy. At the same time it must be clearly understood that eclampsia may be superimposed, theoretically at least, on a "low reserve kidney," a benign hypertension or in a patient with chronic nephritis. These facts must be kept clearly in mind; otherwise the diagnosis may be entirely wrong and the patient suffer because of misdirected therapeutic measures.

In the absence of a known etiology, the treatment of this disease is based on clinical experience and directed chiefly toward measures tending to correct the various abnormal metabolic changes and clinical signs which have been described above. In brief, we employ intravenous glucose because of possible liver damage, for immediate energy requirements and also for its diuretic action, the aim being to reduce the uric acid content of the blood, to minimize liver damage, to reduce edema and to raise the CO_2 combining power. A modified Stroganoff regime of sedation is employed at the same time. With improvement further conservative measures are justified. In our own practice all patients with eclampsia are treated along these lines. In preeclampsia the same therapeutic measures are employed and even if the disease is fulminating in character this expectant treatment is always carried out. In a small percentage of patients where no improvement occurs at the end of twenty-four or forty-eight hours, immediate delivery seems to offer the best hope of success, and in these cases we either induce labor if that procedure is thought feasible with the expectancy of a reasonably short labor, or on the other hand we perform a cesarean section under local anesthesia. If the disease improves with the conservative treatment outlined above, the patient may be allowed to enter labor spontaneously or labor induced at a later elective date when the general condition is usually much improved. Ample statistical evidence has demonstrated that the conservative treatment of eclampsia with convulsions has amply justified that method in contrast to the more radical procedures employed to terminate pregnancy abruptly. During the period from Sept. 1, 1932, to Sept. 30, 1936, Table I illustrates that we cared for 136 patients with preeclampsia and 26 with eclampsia, a ratio of approximately 5:1. There occurred no maternal mortalities in either group; however, because of the relatively small number of patients, this absence of mortality is of no statistical value. Mention of this disease and its significance should also include its more remote effect on the individual afflicted.

Peckham⁴ in 1929 found that 23 per cent of eclamptic patients studied one year after delivery had definite evidence of cardiorenal vascular disease and subsequently after observing some of the same patients for three years or more found that the incidence had risen to 37.7 per cent. The same author also found that 22.6 per cent of patients with preeclampsia when observed over a period of several years

associated with hypertension. On the other hand, the fetal mortality in preeclampsia and especially eclampsia is quite high, the incidence in the latter group usually being quoted as being in the neighborhood of 40 per cent. The maternal mortality in large series of patients with eclampsia is very close to 10 per cent. The immediate mortality in the unclassified group is negligible while in the chronic nephritic group most estimates place the maternal mortality somewhere between 1 and 5 per cent. However, of paramount importance is the fact that the remote mortality during the ten years following delivery in this group of patients is exceedingly high. The significance of accurate diagnoses from a prognostic point of view which also involves advising for or against future pregnancies thus becomes of the greatest importance.

However unsatisfactory this classification is, it does enable us to make fairly accurate diagnoses, sometimes during the antenatal period, in other instances at the time of discharge from the hospital, and at times not until the examination carried out six weeks after delivery or occasionally until months or years have elapsed following the pregnancy in question. Thus it permits us to place in one category patients that have no *immediate* or *remote* mortality from the complication and to place in other groups those patients with possible immediate or remote mortalities due to the disease.

PREECLAMPSIA AND ECLAMPSIA

Our present conception of preeclampsia and eclampsia is that they are one and the same disease, the only essential difference being that the preeclamptic patient has no convulsions. Preeclampsia then is always the precursor of eclampsia. In other words, we have in preeclampsia the clinical picture of eclampsia usually in a milder form with the exception of the convulsions. The clinical features usually are very characteristic and if the patient has been under observation for a sufficient period of time during her antenatal period several important findings arise that facilitate the diagnosis. The disease is usually quite acute, being accompanied by water retention manifested by a generalized edema and a rather sudden increase in weight, a more or less precipitous elevation in both systolic and diastolic blood pressure, and usually a considerable amount of albumin in the urine. Subjective symptoms of the patient are frontal headache, partial or complete amaurosis, vertigo, and epigastric pain. Findings on chemical examination of the blood usually reveal a moderate or marked elevation of the uric acid content, no change at least early in the disease in the nonprotein nitrogen, urea nitrogen, blood sugar or chlorides. The CO_2 combining power is definitely decreased, and the hydrogen ion concentration of the blood tends to be increased. If we superimpose on this picture convulsions with or without coma, we have the eclamptic phase of the disease.

however, in this table are the 92 patients who were followed from three months to three years, and it is seen that in 69 (72.6 per cent) of these individuals, subsequent observations substantiated the original concept of the disease. However, of even more significance is the fact that there were 15 instances where it seemed quite definite that a wrong diagnosis had originally been made and that now we are more or less justified in concluding that these 15 patients have definite evidence of chronic cardiorenal vascular disease. Of note also are the 11 patients that I now categorize as having originally had an "unclassified" toxemia. Undoubtedly, many patients in this latter group will eventually after sufficient observation be classifiable with the group having chronic cardiorenal vascular disease. I should also like to emphasize that even after this relatively long period of observation we are still unable in 11 instances (11.6 per cent) to make a definite diagnosis. It is quite evident from this table that our greatest error in original diagnosis appears to have been in the multiparous patient.

Accordingly, from the follow-up studies of patients who had only a very mild degree of toxemia during the last trimester of pregnancy and whose abnormal findings had returned to normal at the time of discharge from the hospital, we now find 13 (14.1 per cent) with definite evidence of chronic cardiorenal vascular disease and that additional cases have to be temporarily placed in an unclassified group with suggestive changes that will possibly lead to the same diagnosis after further observation. Peekham and Stout² in a follow-up study of a smaller number of patients in the same category but who were observed for a longer period of time, namely, five years, found only one-half normal. The remainder had more or less definite evidence of chronic nephritis and two of their patients had actually died of nephritis in a state of uremia. Their greatest error they found had been made in diagnosing multiparous women in this category and they even go so far as to suggest that the disease entity should be reserved for primiparous women. Accordingly, the outstanding consideration in this type of patient is the all-important fact that a long period of observation is essential before we can be positive of the benign nature of the toxemia in question.

CHRONIC NEPHRITIS

We now approach by far the most difficult group of consideration, namely, those classified as having chronic nephritis, that might more correctly be considered under the general heading of cardiorenal vascular disease. At the outset it is seen from Table I that 1.71 per cent of patients at the time of discharge, fall in this category. We also have referred to the fact that at least 25 per cent of the patients who have had eclampsia or preeclampsia, subsequently develop signs and

subsequently developed signs of changes in their vascular or renal systems. It is not to be assumed that all these patients developed signs of permanent damage solely because of eclampsia or preeclampsia. Some may have had early unrecognizable signs during their pregnancy, but it seems fair to assume that some at least owed the origin of their permanent renal or vascular changes to the eclampsia.

LOW RESERVE KIDNEY

According to the classification referred to above, we classify patients in this group that have moderate elevations of blood pressure, the minimum standard being 140/90 and the maximum usually never above 160/100. There may be no albumin in the urine or only small amounts rarely exceeding 1 gm. per liter. The disease does not become evident until the last trimester of pregnancy and most frequently not until the last month. It occurs with more frequency in the primiparous than in the multiparous woman. As mentioned above, 54.6 per cent of all our hypertensive toxemias are classified in this group. There is no mortality associated with the disease. Its treatment is simple, namely, rest in bed, proper diet, and on occasions induction of labor if the disease is protracted or if there seems to be a danger of the disease's becoming more serious or, in other words, if a preeclampsia becomes superimposed upon this condition.

TABLE II. "LOW RESERVE KIDNEY." FOLLOW-UP OBSERVATIONS OF 150 PATIENTS

Not followed beyond 6 weeks postpartum		25 cases
Insufficient follow-up (less than 3 months)		30 cases
Of these the available data suggest:		
24 are probably low reserve kidney		
2 are unclassifiable		
1 seems definitely nephritic		
3 insufficient data available for classification		
Followed from three months to three years:		
		CASES PERCENTAGE
Low Reserve Kidney		69 72.6
Unclassified		11 11.6
Primiparas	3	} 27.4
Multiparas	8	
Nephritic	15	15.8
Primiparas	2	}
Multiparas	13	
		95

In order to determine how accurate this classification remains after a period of time, when the diagnosis was made at the time of discharge from the hospital, I have recently reviewed the histories of 150 patients delivered during the calendar year 1934 in the New York Lying-In Hospital. The results are illustrated in Table II.

Twenty-five patients in the entire group were not followed beyond the termination of the puerperium, namely, six weeks postpartum. Thirty of the remainder were followed for not more than three months, and four-fifths of these, from the available data, appear to have been correctly classified as "low reserve kidney." Of particular interest,

clarification of the diagnosis in the vast majority of the patients in this group can be arrived at only after a more or less prolonged period of observation and extensive study after the completion of the puerperium.

TABLE IV. CHRONIC NEPHRITIS

Sept. 1, 1932 to Sept. 30, 1936

	FULL TERM	PREMATURE	ABORTION
Total cases	10316	321	699
Chronic nephritis in above cases	133	22	39
Total: 194 cases of chronic nephritis in 11,336 patients			
Incidence: 1.71%			

Table IV subdivides this group of patients according to the period of gestation at which pregnancy was terminated and demonstrates that a relatively large percentage of our patients were delivered prior to viability. In view of the fact that these diagnoses have only been made during the past four years, it is evident that the period of observation and study is as yet much too limited to get an accurate idea of what the ultimate end-results will be. However, it is significant at this time to state that there have already occurred three known instances of death in uremia due to chronic nephritis and that several other patients have marked impairment of kidney function, nitrogen retention, extreme degrees of hypertension or other signs suggesting an extremely unfavorable course.

TABLE V. AGE OF CHRONIC NEPHRITIC PATIENTS

YEARS	FULL TERM		PREMATURE		ABORTION		TOTAL	PERCENTAGE
	SPON.	OPER.	SPON.	OPER.	SPON.	OPER.		
Under 20	1	4	0	0	0	0	5	2.6
20-24	13	3	2	4	2	5	29	14.9
25-29	20	8	4	3	5	7	47	24.2
30-34	25	16	2	2	2	4	51	26.3
35-39	23	10	1	3	4	10	51	26.3
40 and over	7	3	0	1	0	0	11	5.7
	89	44	9	13	13	26	194	

A study of the age incidence of this disease in our material is illustrated in Table V and shows the relatively large number of these cases that we observed below the age of thirty-five years. Of course, the percentage incidence of the disease actually rises with advancing years as is clearly shown in the two groups 30 to 34 and 35 to 39. The number of patients with chronic nephritis in both groups is exactly the same yet the latter group in the clinic population as a whole represents a considerably smaller number of patients. Purely from a statistical point of view it would seem unlikely that many of these patients are suffering from a benign type of hypertension because of the relative infrequency of that disease in young people.

symptoms that place them in this group. I have also already referred to the fact that a considerable number of patients originally classified as "low reserve kidney" also have to be eventually included in this same category. Furthermore, as illustrated in Table III, a study of

TABLE III. "UNCLASSIFIED" TOXEMIA. FOLLOW-UP OBSERVATIONS OF 74 PATIENTS

Not followed beyond 6 weeks postpartum		28 cases	
Insufficient follow-up (less than 3 months)		8 cases	
Followed from 3 months to 3 years:			
		CASES	PERCENTAGE
Unclassified		5	13+
Primiparas	2		
Multiparas	3		
Nephritis		22	58+
Primiparas	3		
Multiparas	19		
Low Reserve Kidney		11	29+
Primiparas	8		
Multiparas	3		
		—	
		38	

the nonclassified toxemias reveals the fact that of the patients that are adequately followed for a sufficiently long period of time at least twice as many will ultimately prove to have evidence of changes in their cardiorenal vascular tissues as will subsequently be found to be normal, multiparous women predominating in the former and primiparous women in the latter group.

An important consideration is to gather some idea of the fundamental underlying pathology in this disease complex. I purposely use this broader name, eardiorenal vascular disease, because we are definitely including patients with very diverse disease entities such as the so-called essential or benign hypertension, some with malignant hypertension and other patients with chronic nephritis as the outstanding findings. In this latter disease some patients have primarily a vascular disease, while in others the pathology originated in the kidney parenchyma itself. In the past with our available information it has often been impossible accurately to classify this complicated group of patients. Possibly in the future with the newer descriptions given us by Volhard⁵ and others, we may be able to differentiate our patients more accurately and accordingly be able to offer a much more accurate prognosis. It does not seem very justifiable from some points of view to include in the same group patients with benign hypertension that may have an expectancy of life possibly up to fifteen or twenty years and patients with pale hypertension as described by Volhard⁵ who have definite chronic nephritis and a relatively short expectancy of life. However, for an analysis of our past experience we will have to be content with the general classification including such fundamental divergent disease processes as I have already outlined. It would seem that the

or some other form of toxemia. The evidence here presented strongly suggests the possibility that the pregnancy itself exerts in some way an action initiating the disease in some instances, and very definitely aggravating the process with an onset prior to the gestation in question in others. With a view to possible clarification of this important point, it would seem significant that if we could prove an increased incidence of hypertension in the female population as a whole, that this might possibly substantiate this observation.

Wetherby⁶ has recently presented a very careful statistical study of the blood pressure in 5,540 individuals of whom 3,258 were women. His conclusions are that hypertension is more common in the female and that it definitely appears earlier in life in the female as contrasted to the male. In fact, he presents statistical evidence to show that the same degree of systolic hypertension is reached in the female during the decade forty to forty-nine years as is manifested in the male twenty years later. It is also, I think, significant to point out that ample evidence has been adduced to show that the disease is somewhat more benign in women as compared to men. Possibly this may be significant when related to the etiology. In fact Blackford and others⁷ in a follow-up study of patients with a systolic pressure of 175 mm. Hg or over found that 70 per cent of the mortality occurred in men yet their patients who were followed from five and one-half to eleven years were predominately women, namely, 65 per cent of the total cases. Other worth-while studies of blood pressure in the apparently healthy group of our population have been made and suggest the same results. No mention is made by Wetherby of the possible effect of childbearing on his findings, nor does he mention the number of women in his study who had borne children. However, he does mention and proves from statistical data that the menopause is not a factor. In view of the fact that his material consisted of a large group of the lower and middle class patients from city and country, and including both housewives and working women, it seems fair to assume that it is at least possible that pregnancy has played some rôle in the production of the hypertension in question.

So little is known of the treatment of this disease that little time need be devoted to the description of that subject. However, in view of the fact that the ultimate prognosis in this group of patients has such grave possibilities and the fact that the fetal mortality is so high, with the known aggravating effect of pregnancy itself, our one consideration of prime importance should be the early diagnosis of the disease and the termination of pregnancy in definitely proved instances and the prevention of future pregnancies under the same conditions. In other words, from an obstetric point of view the treatment of these patients is of value only from a negative point of view, namely, the prevention of a superimposed physiologic function of the normal woman which has a definite detrimental effect on the individual with a known disease of her cardiorenal vascular tissues.

SUMMARY

From a point of view of the prevention of maternal mortality and deaths subsequent to discharge from the hospital, it appears that the prevention of pregnancy in patients with definite evidence of cardio-

The fetal mortality illustrated in Table VI is 12.6 per cent which incidence is nearly 4 times that of the fetal mortality in the clinic as a whole. Of special note in this table is the frequency of deadborn infants which represents over two-thirds of the total fetal mortality. It is my opinion that these deaths are due primarily to the underlying maternal pathology.

TABLE VI. INFANTILE MORTALITY

	FULL TERM		PREMATURE		TOTAL	PERCENTAGE
	SPON.	OPER.	SPON.	OPER.		
Stillborn	2	0	0	0	2	10
Deadborn	3	5	5	1	14	70
Neonatal	1	1	1	1	4	20
	6	6	6	2	20	

Total: 20 infantile deaths in 159 infants (4 twins included)

Note: 2 deaths complicated by premature separation are *included* in the above table. One was deadborn, and one neonatal.

It is also significant that in the total group of 194 patients as reviewed in Table VII the disease was considered sufficiently serious to indicate a therapeutic abortion in 26 instances with sterilization in some cases and without that procedure in others. Twelve others were sterilized at the time of cesarean section. This incidence of sterilization appears relatively small and is in part at least due to difficulties in arriving at the correct diagnosis. However, the remaining patients in this group have been given contraceptive advice.

TABLE VII. CHRONIC NEPHRITIS WITH ABORTION. OPERATIVE ABORTIONS

COMPLETION OF	THERAPEUTIC	THERAPEUTIC AND TUBAL STERILIZATION	THERAPEUTIC AND HYSTERECTOMY	TOTAL
0	12	9	5	26
Total: 26 operative abortions with chronic nephritis				

Of great interest to the obstetrician and internist should be the possible etiologic rôle that pregnancy plays in the production of this disease. Table VIII illustrates the fact that 65 out of the total of 194

TABLE VIII. CHRONIC NEPHRITIS FOLLOWING A PREVIOUS TOXEMIA

	FULL TERM		PREMATURE		ABORTION		TOTAL	PERCENTAGE
	SPON.	OPER.	SPON.	OPER.	SPON.	OPER.		
Chronic nephritis	11	3	1	1	0	10	26	40
Eclampsia	1	0	0	2	1	0	4	6.2
Other toxemia	11	7	0	3	4	10	35	53.8
							65	

patients had a previous toxemia, classified as illustrated in this table. It is significant that only 40 per cent had a previous diagnosis of chronic nephritis while on the other hand 60 per cent followed either eclampsia

INCONTINENCE OF URINE IN THE FEMALE, THE URETHRAL SPHINCTER MECHANISM, DAMAGE OF FUNCTION, AND RESTORATION OF CONTROL*

WILLIAM T. KENNEDY, B.A., M.A., M.B.(TOR.), L.M.C.C., F.A.C.S.,
NEW YORK, N. Y.

(From the Clinic of the Woman's Hospital)

IN A recent publication which was read before this Society last year,¹ the author presented a few observations relating to the damage of the urethra, and concluded that there was a voluntary sphincter situated in relation to the middle third of the urethra in addition to an involuntary sphincter surrounding each of the inner and outer thirds of the urethra. Since that time it has been found that this voluntary muscle exerts but a small force about the middle third and a much greater force about the inner third. H. Dawson Furniss, in a discussion of the author's presentation, showed slides from a recent paper in which H. Martius² described the presence of such a voluntary sphincter. The author, up to the present time, has not made any histologic study of the anatomy entering into these functions, yet he feels, from clinical observations and from the result obtained in the restoration of urinary control, justified in presenting the following analysis of the sphincter mechanism, its damage and its restoration. It will be remembered that in the previous article the author presented evidence that the voluntary sphincter possessed the greatest, and the external involuntary sphincter the least sphincteric control, and that the internal involuntary sphincter was very greatly enhanced by a urethra stricture incorporated in or about it. The author now believes that the external sphincter exerts little force in preventing the escape of urine from the bladder, and also, that the normal internal involuntary sphincter alone may have sufficient power to prevent the escape of urine from the bladder. He now feels, too, that when the free involuntary internal sphincter is enhanced by the normal voluntary sphincter the control is quite positive. The following discussion will serve to clarify these assertions.

THE INVOLUNTARY SPHINCTER (INNER)

In most instances in the body, involuntary muscles are circular and are not attached or fixed at any point, but rather, suspended in some form of a sling. The small intestine lies in a mesentery sling and when the involuntary muscle of the small intestine is damaged and that portion becomes fixed, the remainder of the fibers which function in this

*Read at a meeting of the New York Obstetrical Society, February 9, 1937.

renal vascular disease is not only justifiable but is an essential part of our obstetric care of patients. With this same mind in view it is essential to follow patients with preeclampsia, eclampsia, unclassified toxemia and even the low reserve kidney patients in order to detect early changes in these groups of chronic cardiorenal vascular disease. Furthermore, it is emphasized that we are doing little good in preventing pregnancy in the patient with advanced renal disease whose prognosis is obviously poor, and on the other hand, our utmost efforts should be directed to early diagnosis of the disease and the prevention of pregnancies where further aggravation of the process appears inevitable or even possible.

The prevention of the development of eclampsia by the earlier detection and treatment of the disease in its preeclamptic form should be our constant aim in this type of toxemia. This latter condition has practically no maternal mortality and a low fetal mortality whereas the former has a much higher incidence of both mortalities.

The evidence as presented shows that even in the classification of low reserve kidney or what may be termed in other classifications albuminuria of pregnancy, mild toxemia, etc. are not necessarily immune from the possibility of having some fundamental pathology in their cardiorenal vascular tissues as a sequela, and it is accordingly necessary to have extensive follow-up of every patient no matter how slight the degree of manifestation of toxemia that exists.

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The author observed that a large proportion of women with hypoplasia of the genitalia had mumps during puberty or before this period. Many of these women recall having had pain in the sides during the attack of mumps. Among men it has long been known that orchitis is frequently associated with mumps, but textbooks have very little to say about an analogous condition among women. In men with orchitis there is an interstitial inflammation which, if bilateral, leads to atrophy of the testicles and sterility. The author believes that in young girls with mumps there is a similar interstitial inflammation in the ovary which leads to hypoplasia of the genitalia and sterility. In most of the author's cases there was oligomenorrhea and dysmenorrhea. The outlook for such women is not favorable because the sclerotic changes in the ovaries prevent ripening of the follicles and disturb the internal secretory function of the ovaries.

the rami form in varying degrees from a few scattered fibers to very dense adhesions. The involuntary fibers of the internal sphincter (Fig. 2, *II*) if caught in this damaged area now become no longer able to contract with freedom and whereas it was normally circular it has now taken on a distorted oval form with some fixation at one or more points, and the folds of the urethral mucosa no longer completely fill the urethral canal. This constitutes a larger part of the loss of control. It is not difficult to realize that normal function cannot be restored until these adhesions have been separated and steps have been taken to prevent their re-forming. This must be fortified by some enhancing structure, either a closely related stricture or a slinglike support (Fig. 2, *I*), either fascial or voluntary muscle beneath the involuntary internal

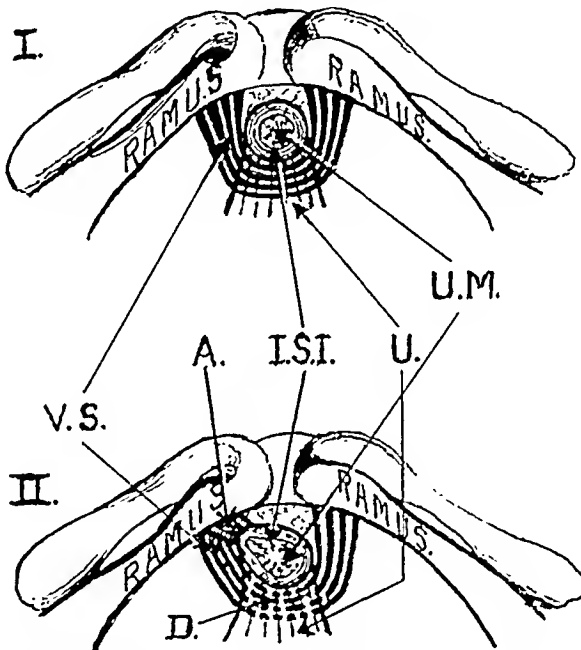


Fig. 2.—The sphincter mechanism. *I*, The normal relation of the voluntary sphincter to the internal involuntary sphincter looking directly into the pelvic outlet from below. *II*, Damaged sphincter mechanism from the same viewpoint. *I*, Normal sphincter mechanism as seen from below, *II*, traumatized sphincter mechanism as seen from below. *V.S.*, voluntary sphincter, *I.S.I.*, internal involuntary sphincter, *U.*, urethra, *U.M.*, urethral mucosa, *A.*, adhesion between internal sphincter and pubic ramus, and *D.*, Splitting of voluntary sphincter fibers.

sphincter muscle. *It is this sling support, which, previously described transplanting operative procedures, have been ingeniously devised to construct.*

THE VOLUNTARY SPHINCTER

This sphincter, like all voluntary sphincters, must have an origin, an insertion, a fascial sheath and a motor nerve supply. Several authors have stated that many nulliparous women, who, having begun to void, are unable to interrupt the flow of urine. This would point to some incomplete development of the voluntary muscle which plays a part in

area lose much of their activity with the result that some degree of stasis or obstruction is established. Pain and discomfort may also accompany this situation. Arteries run in loose areolar tissue between muscles, etc., but when an artery becomes adherent to the healing fracture of a bone or becomes partially incorporated in a longitudinal scar, its contractility diminishes and pain or discomfort may follow. Thus, involuntary sphincters function best (1) when circular (2) without attachments and (3) when suspended freely in a sling. In such a situation do we find the inner involuntary sphincter of the urethra (Fig. 2, I). The weight of the bladder and its contents are partly suspended by the pubovesical ligaments and partly supported by the pubocervical ligaments and their associated vessels (Fig. 1).

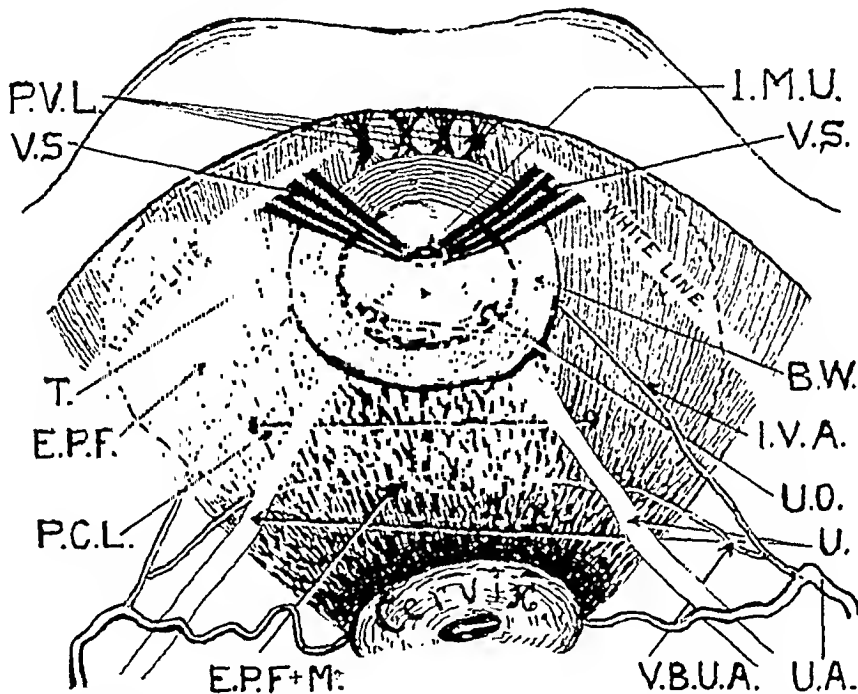


Fig. 1.—Diagram of the anterior portion of the endopelvic fascia with the anatomic structures on its surface, viewed from above directly through the pelvic inlet. *V.S.*, Voluntary sphincter, *P.V.L.*, pubovesical ligament, *P.C.L.*, pubocervical ligament, *I.M.U.*, internal meatus urethra, *T.*, trigone, *B.W.*, bladder wall, *E.P.F.*, endopelvic fascia, *E.P.F.+M.*, endopelvic fascia + muscle, *I.V.A.*, inferior vesical artery, *U.O.*, ureteral orifices, *U.*, ureters, *U.A.*, uterine artery, and *V.B.U.A.*, vaginal branch uterine artery.

The urethra is hanging freely in loose areolar tissue connected to the endopelvic fascia and to the periosteum of the pubis. Now labor comes along. The head is long delayed in the pelvis. Each uterine contraction, first with a pinching of the urethra (rarely the bladder) between the head and one ramus, or, one ramus and the symphysis, or both rami, and second, with an increasing grinding pressure, produces an ecchymosis in the urethral wall and doubtless small hemorrhages between the urethra and the rami. After delivery, organization in this damaged area takes place and cicatricial bands between the urethra and

this support. Joshua W. Davies, who has contributed much to the easy understanding of the pelvic anatomy, and who has helped me much in clarifying the muscular arrangement, believes these fibers to be the anterior portions of the levator muscles. During labor this sphincteric support may suffer damage by breaking the fibers near their insertion in the median raphe. Hence the "sagging" of the urethra as described by B. P. Watson. Thus, the loss of voluntary sphincter control consists of damage of the voluntary sphincter in or near the midline. To restore this sphincter control one must remove the damaged portion of the voluntary sphincter and approximate in the midline the remaining—fortunately little damaged—portion of this voluntary sphincter.

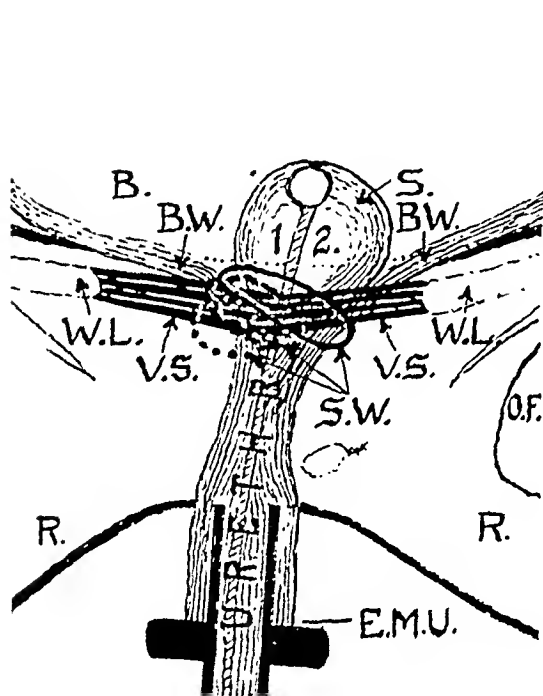


Fig. 4.

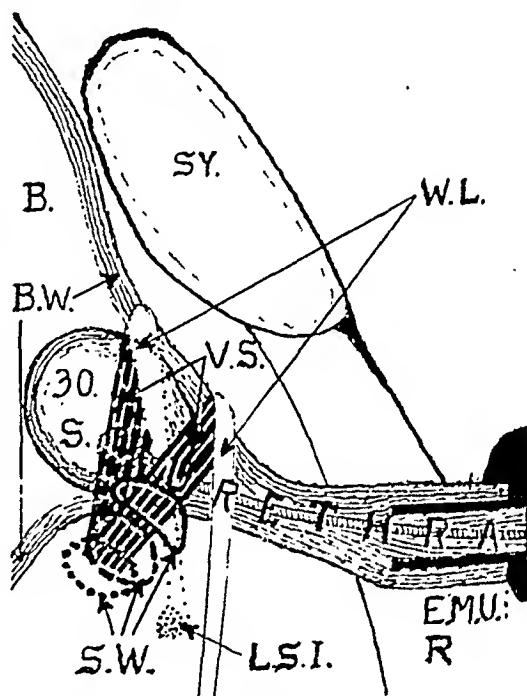


Fig. 5.

Fig. 4.—Drawing from a roentgenogram of the sac in the urethra and bladder, after operation, before the silver wires have been removed (anteroposterior view). V.S., Voluntary sphincter, W.L., white line, S.W., silver wire—over median raphe S., urethral sac, R., ramus pubis, B., bladder, B.W., bladder wall, O.F., obturator foramen, and E.M.U., external meatus urethra.

Fig. 5.—Drawing from a roentgenogram of the sac in the urethra and bladder, after operation, before the silver wires have been removed (lateral view). V.S., Voluntary sphincter, S.W., silver wire over median raphe, W.L., white line, B., bladder, B.W., bladder wall, S., urethral sac, L.S.I., left spine ischium, SY., symphysis, E.M.U., external meatus urethra, and R., ramus.

THE SPHINCTER MECHANISM

When an operation (1) separating the urethra from both rami and plicating the urethral wall in the midline to prevent the reattachment of the urethra to the rami and (2) restoring the practically undamaged portions of the voluntary sphincter (levator fibers) beneath the urethra has been done, one is happy to find that incontinence can be discontinued and sphincteric control can be established. The author, there-

sphincter control. One might here deduce that such a muscle having its origin laterally to the urethra and its insertion in a midline raphe had not been completed during fetal development. Such a condition would predispose to a partial potential loss of sphincter control. From experience, one who has had the misfortune to produce incontinence more than once in patients who were operated upon for a cystocele, is chagrined that he has damaged some part of the sphincter control. Since the urethra did not seem to have been exposed, he felt that he had severed the voluntary fibers below the urethra and had failed to restore them when the incision beneath the urethra was closed. Let us look at the anatomy behind the symphysis and combine it with our findings at operation. After one separates the urethra from the ramus, places a finger on the posterior of the symphysis laterally and makes traction on

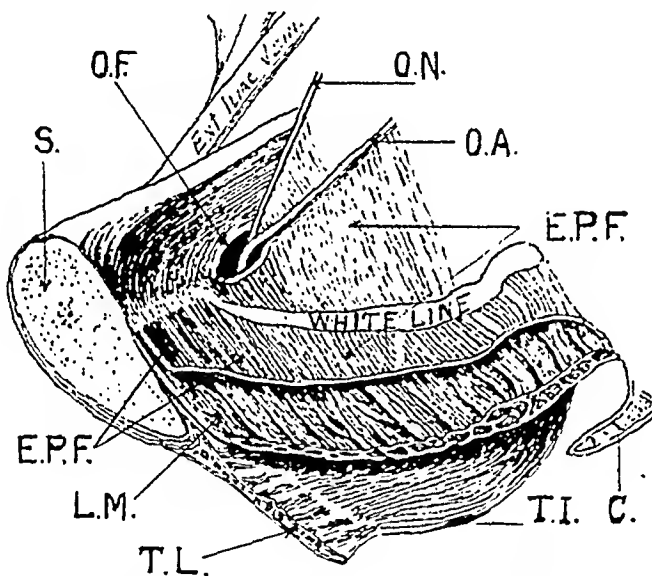


Fig. 3.—Anatomic structures posterior to the symphysis (From Cunningham). L.M., Levator muscle, E.P.F., endopelvic fascia, T.L., triangular ligament, S., symphysis, T.I., tuberosity ischium, C., coccyx, O.F., obturator foramen, O.A., obturator artery, and O.N., obturator nerve.

that portion of the vaginal wall lateral to the urethra and high up in the vestibule, one feels there is some pulling from a fixed point which seems to be the white line (Fig. 3). Fig. 3 illustrates the anatomical structures posterior to the symphysis pubis. From this point come off only the levator fibers in their sheaths, and it is quite possible for one from each side to join in a median raphe beneath the urethra. If so, where do they come relative to the urethra? Having used silver wire, it was possible to photograph the bladder and the urethra after the method in the author's previous article. An anterior view is shown in a drawing from such a roentgenogram as shown in Fig. 4. If one outlines the white line and draws lines from each to a median raphe (the silver wires) we see a urethral support which passes beneath the inner third of the urethra. A drawing from a lateral roentgenogram (Fig. 5) similarly illustrates

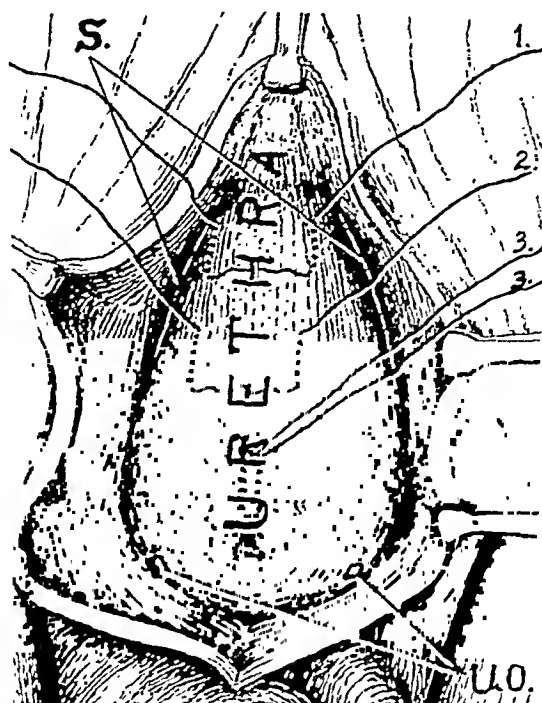


Fig. 7.—Drawing to show the urethra separated, from both rami of the pubis. Mattress sutures have been placed to enfold the urethral wall, thus strengthening more or less its damaged structures. 1, 2, 3., Mattress No. 1 chromic catgut sutures, 3. is tied; S., separation—urethra from ramus of pubis (bilateral); U-R-E-T-H-R-A, urethra from internal to external meatus; U.O., position of ureteral orifices; and U., position of internal meatus, urethra.

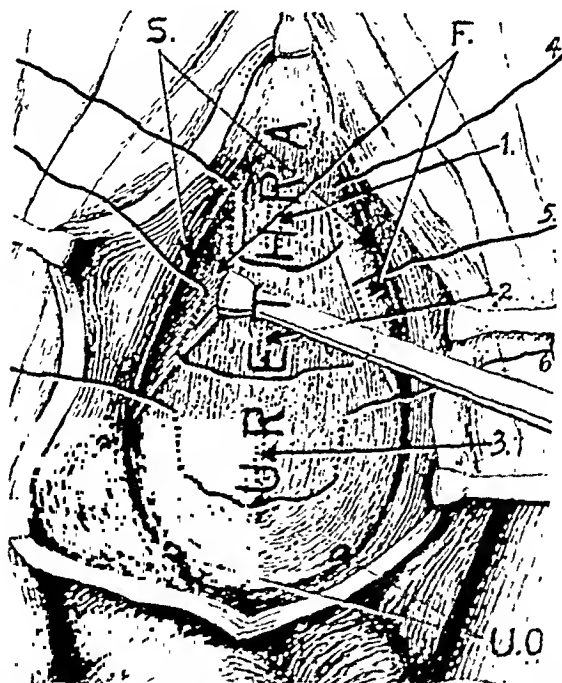


Fig. 8.—Drawing to show the first row of mattress sutures tied and the second row of mattress sutures placed to further enfold the urethral wall and to bring the undamaged urethral wall under the urethra. The urethra cannot now reattach itself to the ramus of the pubis. Its wall is now undamaged urethral structure. 1, 2, 3., First row of mattress No. 1 chromic catgut sutures tied, S., separation—urethra from ramus pubis (bilateral), F., smooth tensile fascialike tissue on wall of urethra (undamaged), 4, 5, 6., second row of mattress No. 1 chromic catgut sutures placed, U-R-E-T-H-R-A, urethra from internal to external meatus, U., position of internal meatus urethra, and U.O., position ureteral orifices.

fore, defines the sphincter mechanism as the free internal involuntary sphincter muscle supported and enhanced by the voluntary sphincter muscle sling containing levator muscle fibers (see Fig. 2, I).

OPERATION FOR THE RESTORATION OF SPHINCTER CONTROL

Each labium is fastened laterally to the skin by a suture. A perineotomy is done when necessary, to sufficiently expose the anterior vaginal wall for a cystocele operation. The midline anterior to the cervix is incised, exposing the lower portion of the bladder. The bladder is removed from the cervix and the vaginal wall then separated from the bladder laterally as far as the rami and forward to about 1.5 cm. from the external meatus of the urethra. By a blunt dissection (Fig. 6), the urethra is separated from the median posterior margin of the ramus (keeping extremely

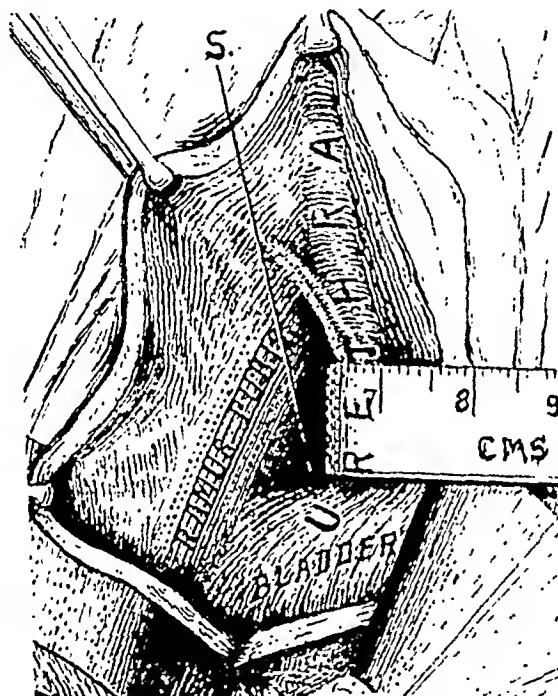


Fig. 6.—Drawing to show the urethra removed from the right ramus of the pubis. The separation has been carried back into the paravesical space, a distance of about 6 cm. *U-R-E-T-H-R-A*, urethra from internal to external meati, *S*, line of separation into paravesical space freeing the urethra from the ramus pubis.

close to the ramus) and the separation carried into the paravesical space, which is about 6 cm. The same dissection is repeated on the opposite side, after which the urethra becomes entirely free laterally. Sometimes in this separation, one may encounter a branch of the inferior vesical artery which is usually on the bladder and should be ligated. Three mattress (No. 1 chromic catgut) sutures, 1, 2, 3, are placed as shown in Fig. 7, 3, in the diagram having been tied. 3 is placed just above the internal meatus of the urethra, indicated by the *U* in *U-R-E-T-H-R-A* in Fig. 7. These sutures are tied and held for traction. When traction is made, one now observes that there is a smooth, very tensile wall of the urethra which has apparently never been damaged. Sutures 4 and 5 as shown in Fig. 8 must be placed so that when they are tied, this structure meets its opposite mate in the midline. Suture 6 will simply plicate the lower portion of the urethra. The vaginal wall is then cut so that when approximated in the midline there will be little

redundancy. The vaginal wall high up in the vestibule is now grasped with an Allis clamp (Fig. 9) and pulled out to see the highest dimple, through which the needle on the silver wire, 7, is passed, very close to the margin of the ramus. It is carried over and out at a corresponding point on the opposite side. This tissue has in it the fibers of the voluntary sphincter as shown in the insert in the corner of Fig. 9. Two other silver wire sutures, 8 and 9, are placed as illustrated. The midline is then closed with interrupted No. 2 chromic catgut sutures. The silver wires are approximated gently and twisted each to its opposite, and the finished anterior urethral wall is illustrated in Fig. 10. A shot is placed on the long end of all six wires together. A No. 14 male catheter is placed in for retention and left in about six days. The silver wires are removed about the twelfth day. Should any irritation of the trigone manifest itself while the catheter is in situ, the connection to the catheter is removed and one ounce of a freshly made 5 per cent solution of papain is put into the bladder through the catheter, the catheter clamped for two hours, then reconnected. This should be repeated once each day for two or three days. After the catheter has been removed and the patient is voiding normally, but there is a trigone irritation, the catheter should be passed, the bladder emptied and the papain solution instilled once each day for three days.

RESULTS

For convenience in analyzing a group of 28 consecutive cases to give one a cross-section of the type of cases, the author has divided them into seven groups:

- Group 1: Patients whose major complaint was incontinence and who had minor complaints which also needed relief, were 23.
- Group 2: Patients who had stress incontinence associated with some degree of prolapse, cystocele, etc., were 5.
- Group 3: Patients twice or more operated upon for relief of incontinence, were 2.
- Group 4: Number of patients operated upon once before for incontinence were 3.
- Group 5: Number having incontinence more than two years, were 14.
- Group 6: Number who had incontinence for a number of years and for two years or more had lost the sensation of control or voiding, were 3.
- Group 7: Number who had an adherent retroversion studded with myoma was 1 (appears also in Group 2).

COMPLICATIONS

First, in Group 1 (also appears in Group 5) was one patient who was operated upon for incontinence of urine, cystocele, first-degree prolapse, lacerated pelvic floor, and rectocele. After the catheter was removed about the tenth day she was unable to void, was catheterized for about eighteen days (she was taught to catheterize self). Five weeks after operation she was cystoscoped by Dr. George Hoch. There was no stricture found but the trigone had raised edematous longitudinal folds which evidently prevented the muscular opening of the internal meatus. This patient catheterized herself for three weeks more, then began to void and is now voiding and completely continent.

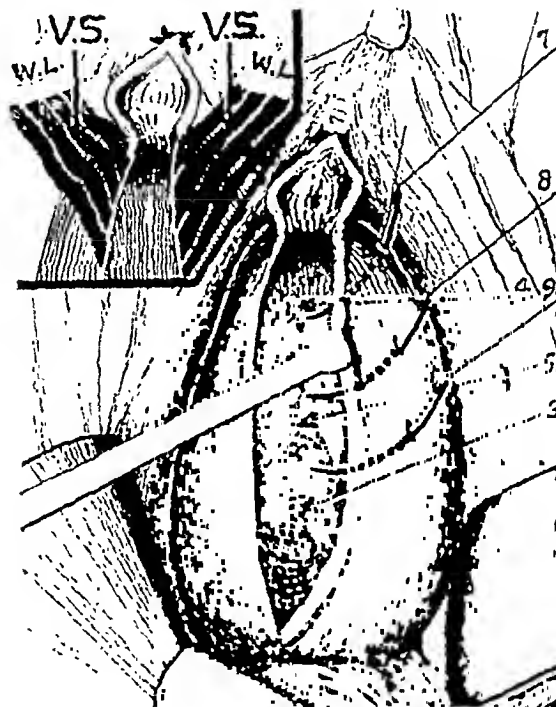


Fig. 9.—Drawing to show the vaginal wall after the damaged portion has been removed. The voluntary sphincter is being drawn together with silver wire. The first wire is passed laterally and anteriorly as far as possible, to grasp the undamaged retracted fibers. Position of fibers is shown in the insert. 4, 5, 6., Second row of mattress No. 1 chromic catgut sutures tied, 7, 8, 9., No. 26 silver wire sutures, V.S., voluntary sphincter, W.L., white line, and Insert, showing position of voluntary sphincter fibers.

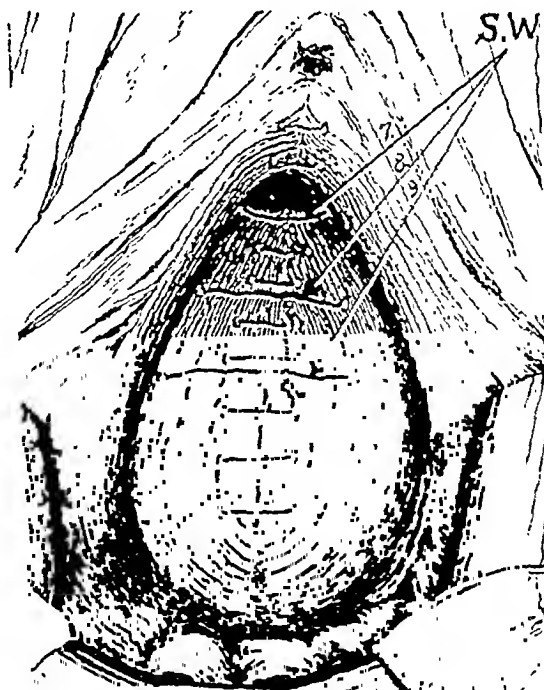


Fig. 10.—Drawing to show all sutures tied. Interrupted catgut sutures approximate the margins of the vaginal flaps. Silver wire sutures are approximated and twisted to hold the voluntary sphincter fibers. Vaginal wall closed, interrupted No. 2 chromic catgut; 7, 8, 9., silver wire No. 26. Sutures twisted; and S.W., silver wire.

but it is most likely, because usually from my observations in the follow-up clinic, a permanent incontinence begins before four weeks after the operation is done.

Of 28 patients, 26 have had urinary control restored, one has an incontinence which may not be permanent and one has sufficient incontinence to lead one to believe she may require a second operation.

CONCLUSIONS

1. From observations in this study one may describe the sphincter mechanism as made up of a free involuntary sphincter surrounding the inner third of the urethra, supported and enhanced by a voluntary sphincter composed of the anterior portions of the levator muscles, which unite in a median raphe beneath the urethra. Since in the previous article the greater sphincteric force was found to exist about the middle third of the urethra one may deduce that the above sphincter mechanism also lies around and beneath the middle third, having more and stronger fibers in this location.

2. That a woman who has never had a labor but who begins to suffer a partial incontinence of urine due to loss of sphincter control may have had an incomplete union of the fibers composing (1) the involuntary sphincter and (2) the voluntary sphincter.

3. That labor may injure (1) separately the involuntary sphincter by directly or indirectly causing it to be distorted and fixed to the ramus of the pubis, thereby very markedly diminishing its function as a sphincter and (2) separately the voluntary sphincter by splitting its fibers parallel to the urethra in or adjacent to the median raphe and (3) conjointly at the same labor (1) and (2).

4. That the most difficult cases, namely, those previously operated upon for incontinence of urine and those who had lost sensation of control or voiding, all had continence restored.

5. That the only complete failure was one whose operation was followed by an infection in and sloughing of the anterior vaginal wall.

6. That since the method offered to restore continence of urine is followed by a reasonable degree of success, one might logically deduce that the description of the sphincter mechanism was nearly correct.

The author expresses his appreciation to Dr. George Gray Ward, Chief Surgeon of the Woman's Hospital, for the privilege of carrying on this work and to Dr. Edward A. Bullard for assigning him so many of these cases.

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Second, in Group 1, there was a patient who had to be catheterized for about twenty-four days, then she began to void but had from 4 to 6 ounces' retention. This diminished and she went home. The Visiting Nurse Service catheterized her each afternoon for about ten days. She, having a fair degree of intelligence, was taught to catheterize herself and eight weeks after the operation she began to void and has done so since. She also is completely continent.

Third, in Group 7, the patient presented a difficult operation. A uterus retroverted in third degree and studded with myoma had lowered the vitality of the vaginal wall posteriorly. The urethra was densely adherent to the right ramus for about 1 cm. In separating the urethra from the ramus a large opening was made into the urethra and this was closed with a running mattress suture. The uterus was removed, the urethra pliated and the urethral portion of the vaginal incision closed with silver wire and interrupted catgut. The bladder and cervical portion of the anterior incision were closed with interrupted catgut; a rectocele and pelvic floor were repaired and a retention catheter put in the urethra. On the tenth day, urine appeared constantly on the pads, and it was found that the posterior portion of the anterior wall incision had broken down. This was treated daily and on the eighteenth day urine came only through the catheter. Five days later the catheter was removed and the patient apparently had continence and was allowed to go home. She returned in about one week, quite incontinent, and was readmitted to the hospital for a study. Using indigo carmine and observing the vagina and urethra, the urethra seemed to be the only escape of urine. By treatment, this patient can be dry for periods varying from half an hour to two hours. Nevertheless, I believe that this patient will need a second operation later and, fortunately, she is the only one in the group of 28 patients who shows any sign of needing further operative procedure.

Fourth, in all groups, about half of the patients, at some interval after removal of the catheter, presented symptoms of a moderate trigonitis lasting for four or five days. This was relieved by a daily instillation into the empty bladder of an ounce of a 5 per cent solution of papain.

URINARY CONTROL

Strange as it may appear, in Groups 3 and 4, and 6, which comprised all the patients who had been previously operated upon for ineontinence and those who had lost all sensation of control or voiding, now have normal control of their urine. There are two patients who have some degree of ineontinence: (1) the one in Group 7 described in detail above and (2) another from Group 1, who was continent for two and one-half months, then contracted a cold and suddenly became partially ineontinent. Whether or not this may be an urgency could not be ascertained,

ing the vesical neck. She had complete incontinence and obvious relaxation of the vesical neck. On cystoscopic examination nothing was noted in the bladder at any time. She was referred to Dr. Kennedy who cured her incontinence by operation.

DR. HENRY D. FURNISS.—It seems to me that this procedure is largely an extension of the Kelly operation. I doubt the wisdom of such a wide dissection as with less dissection you can, as a rule, get the same results. Dr. Kennedy's first sutures go pretty well back on to the bladder, which may account for some of the retention.

It is well to operate with a Pezzer catheter in the bladder. By pulling it forward you can determine the location of the internal sphincter. The sutures should infold the vesical neck and also the urethra.

Kelly originally advocated silk, which is admirable, unless you get an infection. I believe we have a superior suture material in fine stainless steel wire (33 gauge); steel wire is easily tied and can be left in situ as it causes no irritation, and there is less chance of infection than from catgut or silk. I believe catgut is a very unsafe material to use, especially chromic catgut.

There is a class of case in which I do not think a vaginal type of operation is suitable: in women with a very thin atrophic vaginal wall. There isn't enough thickness of the vaginal mucosa to get a good result. Such cases are best repaired by infolding the sphincter and the urethra through a suprapubic incision. This can be done extraperitoneally, and with almost no bleeding. The bladder sphincter lies out in the wound and sometimes the operation is a bit difficult.

By infolding the bladder and going as far back as Dr. Kennedy does, one runs the risk of injuring a ureter. I had such a misfortune. In that particular case I did not use a Pezzer catheter but went back too far, and injured the left ureter, producing a uretero-vaginal fistula.

DR. MAX D. MAYER.—Some years ago, after a careful follow-up of all our plastic material at the Mt. Sinai Hospital, we were somewhat disappointed at the results of the operation for incontinence that we were using at that time. In particular it was found that our attempts at cure of the incontinent cases where there was very little or no cystocele were unfortunate. Starting in January, 1935, then, an attack was made on this problem from three directions. We tried, first, to eliminate those cases of incontinence that were not based on an organic ground, by investigating the mental component. A certain percentage of cases were thus at once eliminated, for it was found that much could be done by treating those patients on a nonorganic basis. The second approach was by the cystoscope and local treatment. The third was by a revision of our operative technique.

Our results from January, 1935, for the subsequent eighteen months were considerably improved. In 50 cases we had cures in all but 5, and when an operation was performed, which was very similar to the one Dr. Kennedy described, we succeeded in curing 19 out of 20 cases. The operation that we do is somewhat simpler in technique. The incision is carried forward in the anterior vaginal wall to about a half centimeter from the external meatus, the pubo-cervical fibers, the bladder pillars, are exposed as well as the entire urethra and mobilized for the inferior two-thirds of its circumference. The tissues are pushed back to and behind the pubis until they cannot be pushed back any farther. This clearly delineates the uretero-vesical junction. The bladder is then pushed back and anchored back by suture of the pubo-cervical fascia, which is attached to the cervix. Then a stitch, very much like the Kelly stitch, is placed, catching the sphincter, and then from that point forward the urethra is freed for its entire length and infolded by sewing over the suburethral fascial structures. We believe that this mobilization of the

DISCUSSION

DR. THOMAS C. PEIGHTAL.—About a year ago Dr. Kennedy demonstrated his operative technique to us at Roosevelt Hospital and since that time we have practiced it in 18 cases. In 3 of these there was no incontinence, but the cystocele was accompanied by marked sagging of the urethra, which it appeared could be supported best by Kennedy's method.

In the other 15 cases there were varying degrees of incontinence, 5 of them having had previous unsuccessful operations for incontinence. Three of these 15 incontinent cases were done too recently to be considered in measuring operative success but of the other 12 patients, who have been out of the hospital now for from four to twelve months, 11 are continent and one leaks occasionally on severe coughing.

The complications which we have met are roughly of two kinds, one due to operative injury of the urethra and the other to subsequent cystitis and pyelitis. Of the first type there were 2 cases. In one in which the urethra was torn at operation and immediately repaired, there was sufficient stricture with some bladder residue to require catheterization and postoperative dilatation of the urethra for several weeks, but this patient now voids without residue and has satisfactory control. The other patient developed a small urethrovaginal fistula in the middle third of the urethra due to one of the supporting "sling" sutures of black silk sloughing into the urethra following operation. This fistula was successfully closed without further difficulty five months after her operation and this patient now has good continence.

The other complication, cystitis or pyelitis, occurred in 3 patients, but all 3 are now well and continent. As all these patients had an indwelling catheter for from one to two weeks, this complication was altogether likely. We feel that, as one develops his skill in this technic and carefully organizes the postoperative care, these complications will occur much less frequently.

The most important step of the whole technique is the free mobilization of the periurethral tissues from the rami of the pubic bones. When this is freely accomplished the defect in the tissue beneath the urethra becomes more apparent and one, two, or even three layers of infolding sutures may be placed without undue tension. The building up of such a urethral support is possible only when all adhesions to the pubic arch are thoroughly freed.

In considering the postoperative treatment one should give due consideration to the length of time the indwelling catheter is to be allowed to remain in the bladder. The purpose of its use has been served as soon as the postoperative periurethral swelling has receded to the point where voiding is possible. In our early cases we kept the catheter in place for two weeks, but more recently we have found it can be removed, in the majority of instances, in from six to eight days. One must then catheterize these patients periodically as not all begin to void at once; and catheterization should be done for a few days after voiding begins, to be certain no bladder residue develops. These are minor points, but all are important from the standpoint of comfort and smooth convalescence.

DR. GEORGE F. HOCH.—From the urologic standpoint, I think it is quite important that all these patients, prior to having any operative work done on them, should have a complete urologic study because not infrequently an incontinence is merely an urgency that may be due to some disturbance in the bladder, such as tumor or renal tuberculosis.

The opposite situation may also exist, such as a recent case I have seen, which a urologist had been taking care of for three years, treating her bladder, even so far as fulgurating points in the bladder, which he said were inflamed, and also fulgurat-

hundred cases of this operation for the cure of cystocele, performed by me, were taken from the records of the Woman's Hospital for study and review. Beginning with March 23, 1926, the cases were taken consecutively and the one hundredth patient was operated upon Dec. 3, 1930, a period of three years and nine months. These patients had follow-up records ranging from three months to eight years after operation.

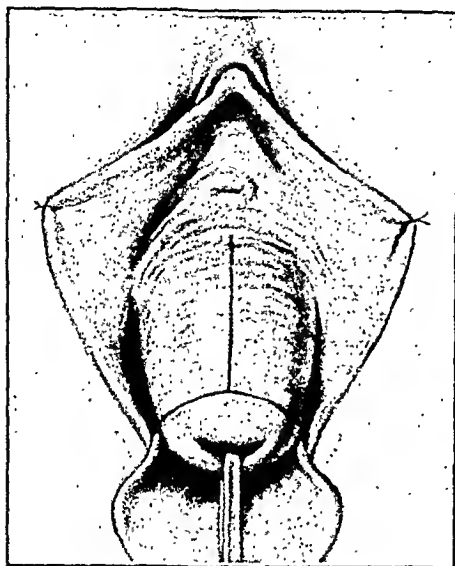


Fig. 1.

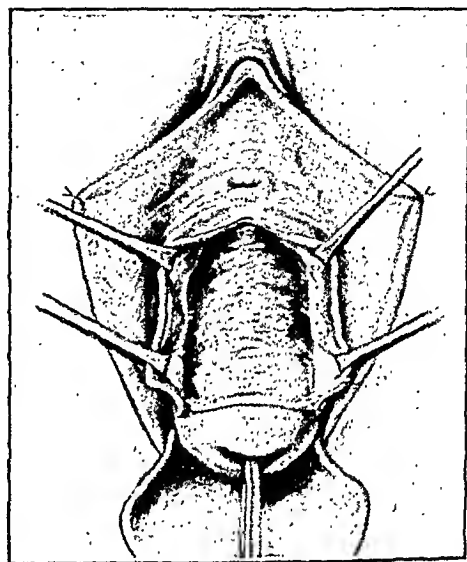


Fig. 2.

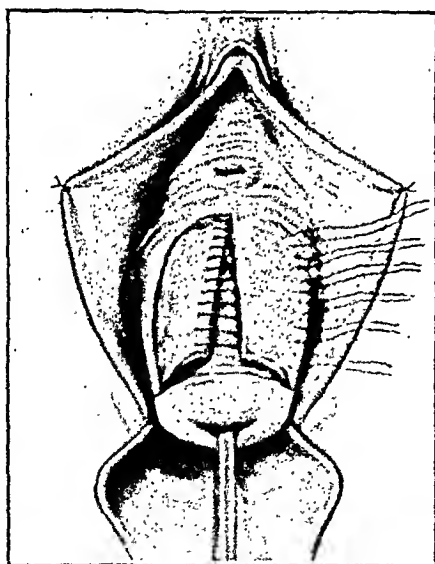


Fig. 3.

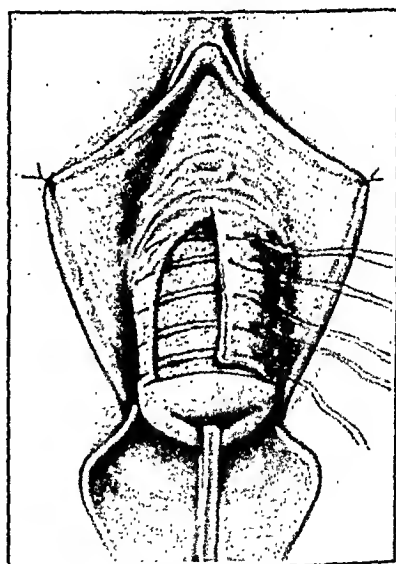


Fig. 4.

The ages of these patients ranged from the youngest, of 31 years, to the oldest, of 70 years.

The operative procedures followed in this series of cases were as follows: The uterine canal may or may not be curetted, depending upon symptoms present and also the age of the patient. The cervix of the uterus is amputated in all cases, either at the internal cervical os or below this

urethra, permitting it to go up when the bladder is pushed up, is an important feature in the good result, and also that this suture at the uretero-vesical junction acts as a sort of organic pessary.

The factor of voluntary control, in addition to the involuntary control, is most important. For a while, when the involuntary control is lost, due to a birth trauma, there may be compensatory function of the voluntary control so that the effect of the birth trauma may not be noted till many years after a childbirth. Then, with asthenia or intercurrent illness, or progression of prolapse or cystocele, the latent lesion is made manifest. It is for that reason that with complete restitution of the voluntary control, in addition to the strengthening of the involuntary control, we feel it is important, in addition to the simpler procedure we use for the cure of the anterior vaginal wall, to add a perineorrhaphy and restitution of the posterior portion of the levator function.

DR. HERMAN GRAD.—To appreciate this operation for incontinence one really has to see it done, and then he is surprised at the extensive dissection that is necessary to free the urethra from its adherent position. The success of the operation depends on this careful dissection.

DR. WILLIAM T. KENNEDY.—I wish to thank Dr. Peightal for his support of my findings. His results compare with mine, so that I feel, while the last word has not been said on this subject, yet the direction in which we are going is the right one.

THE BISSELL OPERATION FOR CYSTOCELE*

HERMANN GRAD, M.D., F.A.C.S., NEW YORK, N. Y.

(From the Clinic of the Woman's Hospital)

THIS paper is presented as a memorial to a former distinguished member of this Society, Dr. Dougal Bissell, who died in 1935. He devised an operation for the cure of cystocele, which he described in a paper before this society in 1918. I wish to present before you a study of 100 cases of this operation. Dr. Bissell named the operation the "fascia lapping operation for the cure of cystocele," but in later years admitted that it was not fascia but vaginal wall which was pliated. The operation consists of ineising the anterior wall of the vagina from the meatus to the cervix in the midline, as shown in Fig. 1. The anterior vaginal wall is then freed from the bladder by entering the nonvasculo-reticular layer of tissue between the bladder and the vagina, as shown in Fig. 2. The anterior vaginal wall on the right side of the patient is then denuded of its mucosa and the denuded part pliated under the left half of the vaginal wall, like buttoning up a double-breasted coat. The denuded portion of the vagina is sutured into position by chromic gut, the suture being passed in the left sulcus of the vagina (Fig. 3). The left side of the vaginal wall is then sutured snugly over the right half (Fig. 4). Fig. 5 shows the completed operation. One

*Read at a meeting of the New York Obstetrical Society, February 9, 1937.

needs no further operation. The follow-up in these 100 cases demonstrated that if the Bissell cystocele operation fails to cure, the failure will become manifest during the first three months after the operation.

The failure in all three cases was due to an inflammatory reaction that followed the operation, including high temperature, bleeding, early absorption of the catgut and failure of complete union of the plicated and sutured parts.

TABLE I. ONE HUNDRED CASES OF CYSTOCELE AND ASSOCIATED LESIONS

First degree prolapse	20 cases
Second degree prolapse	2 cases
Third degree prolapse	14 cases
Cystocele	100 cases
Rectocele	79 cases
Lacerated pelvic floor	86 cases
Lacerated pelvic floor complete through sphincter ani	3 cases
Lacerated cervix	43 cases
Urethrocele	15 cases
Hypertrophy of cervix	18 cases
Carcinoma of cervix	1 case

TABLE II. OPERATION FOR THIRD-DEGREE PROLAPSE

Vaginal hysterectomy	
Mayo technique	
Bissell cystocele repair	6 cases
Emmet-Goff pelvic floor repair	42.2 per cent
Watkins interposition	
Amputation of cervix	
Bissell cystocele repair	1 case
Emmet-Goff pelvic floor repair	
Amputation of cervix	
Bissell cystocele repair	7 cases
Emmet-Goff pelvic floor repair	14 cases
<i>Reason for Vaginal Hysterectomy</i>	
Myoma uteri	2 cases
Suspected malignancy	2 cases
Extreme eversion of vaginal wall	2 cases
	6 cases

The technique of the Bissell operation is not difficult to master, and when acquired, the operation is easily performed. It is not time consuming, and if the technique is followed, the depth of the vagina is not shortened but rather lengthened. The operation restores the anterior wall of the vagina to a normal appearance and gives excellent symptomatic cures. I recommend this operation very highly. It gives excellent results in a very large percentage of cases.

point, depending upon the length and hypertrophy of the organ. The canal sutures are placed on the right and left side of the cervix, instead of anteriorly and posteriorly. The cystocele is then repaired as described by Bissell. The rectocele is repaired by a few sutures in the fascia of the levator ani muscle and the urethrocele by the Kelly stitch. The perineum is then repaired by the Emmet or Hegar method so ingeniously improved by our worthy member, Byron Goff. If a complete tear is present, silver wires are used in the sphincter ani, otherwise, chromic cut is used throughout the entire operative field. In two cases, in this series, a Watkins interposition was also performed.

In the series of 100 cases, there were 36 cases of procidentia uteri, as shown in the table. Fourteen of these cases were third-degree prolapse. In 6 of the 14 cases, or 42.2 per cent, of complete prolapse, a

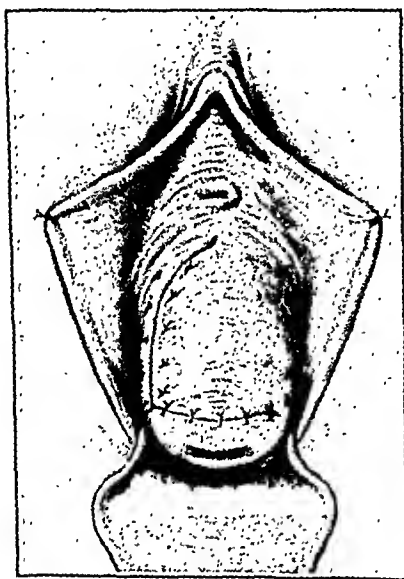


Fig. 5.

vaginal hysterectomy was added to the operative procedure outlined above, and in one case, a Watkins interposition was performed. The reasons for vaginal hysterectomy in the 6 cases of complete prolapse were as shown in Table II.

END-RESULTS

There were 97 anatomic restorations of parts with symptomatic cures. The subsequent history in the three cases where the operation failed were as follows: One patient was reoperated upon a year after the first operation. A Bissell cystocele operation was again performed. This time the operation succeeded in curing the patient. In the other two cases, one is now able to wear a pessary which gives her complete relief. Before this operation she was unable to wear any pessary at all. The second patient has a sagging of the cystocele, but is symptom-free and

permanence of "cure" is thought to be equally as good as that obtained by surgical methods. In looking over our files for the years 1918 to 1927 inclusive, a ten-year period, we find, that of 1,433 cases of carcinoma of the cervix seen on the Gynecological Service, 1,395 cases were grouped as primary and recurrent cases. In January, 1937, ten to nineteen years later there were 144 patients or 10.2 per cent of these groups still alive. This does not represent the entire ten-year survival rate, but merely gives the number surviving in 1937 and is of interest as an indication of the permanence of cure by radiation methods.

TABLE I. CARCINOMA OF THE CERVIX 1918-1927

CASES SEEN		ALIVE IN 1937
Primary	1,129	118
Recurrent	266	26
Prophylactic	38	14
Total	1,433	158

During the last two decades, many changes have been made in our radiation methods for the treatment of cervix cancer. First, radium alone was used, in the form of the element and placed against the lesion or into the cervical canal. Later it also was applied externally about the pelvis in the form of radium packs. Credit is due the late Dr. Harold Bailey for establishing methods of cross-firing the diseased area by radiation. Still later, bare glass tubes containing the radium emanation were implanted in the periphery of the cervix in order to give a more uniform dose. This method was discarded when we learned how to make the gold filtered radon seeds in use today. In 1922, external radiation in the form of low-voltage roentgen therapy, in combination with the direct application of radium, was introduced as a routine procedure in our clinic. In 1926, high voltage roentgen therapy represented by the 200 k.v. machine was instituted. This voltage has continued to be our standard to the present. For a short period of time in 1931, and 1932 a few patients were treated by roentgen rays generated at 700 k.v. peak. The number, however, was too small to be of statistical value, even though the encouraging results obtained would suggest that super-voltage machines may have distinct value in selected cases. These forms of external radiation are used in an effort to increase the amount of effective radiation delivered to outlying parts of the pelvis not affected by radium applied to the cervix.

During the years under consideration in this report, i.e., 1928 to 1931 inclusive, the usual procedure consisted of a preliminary cycle of roentgen therapy delivered through 4 pelvic portals measuring 15 by 10 cm. One portal was treated daily with a dose of 750 r. The physical factors were: 200 k.v. (peak), 4 or 30 ma., 50 cm. T.S.D. and $\frac{1}{2}$ mm. en. filtration. The beam was directed toward the parametrium so that this region was cross-fired without cross-firing the bladder and rectum.

METHODS AND RESULTS OF TREATMENT IN CARCINOMA OF THE CERVIX AT THE MEMORIAL HOSPITAL*

WILLIAM P. HEALY, M.D., AND E. L. FRAZELL, M.D., NEW YORK, N. Y.

THE diagnosis and treatment of carcinoma of the uterine cervix present one of the more important medical problems with which we are confronted. In spite of increased prophylactic procedures, increased diagnostic acumen among physicians in the early recognition of the disease, and augmented facilities for therapy, the yearly death rate is still high. Hoffman¹ finds it to be 12.1 per 100,000 in the United States. There is reason to believe that these figures are too low. Pack and Lefevre² found that carcinoma of the cervix comprised 24.94 per cent of all cancers in females admitted to the Memorial Hospital. This was 11.16 per cent of all cancer admissions.

Etiologic factors of trauma incident to childbearing, unrepaired cervical lacerations, and chronic inflammatory conditions are well known, but earnest efforts by surgeons, gynecologists, and obstetricians to remove these factors do not seem to be reducing materially the incidence of cancer of the cervix. This report shows but slight increase in the percentage of early cases seen. The routine use of the Schiller test and the colposcope may bring some improvement, but those who have used these tests are not uniform in their commendation. Unfortunately in our work we rarely see cases which require these refinements of diagnosis as the diagnosis is usually obvious when the patient is referred to us.

The object of this report is to bring up to date the most recent five-year end-results obtained at the Memorial Hospital and to discuss some of the problems encountered in treatment. The number of patients seen and treated in our clinic is large enough to enable us to draw some conclusions which we hope may be of value to others. Because of the unusual facilities of the institution, we are able to try different forms of therapy on sufficient numbers of cases in an attempt to determine their relative value.

Radiation has been our method of choice in all cases of cancer of the cervix for the past twenty years. Radiation, with its low primary mortality, and its offer of cure to a larger percentage of all cases, has distinct advantages over the radical Wertheim operation. Also the increased number of men capable of administering radiation and the comparable results obtained by it, in the operable group of cases, have given it a dominant position in the treatment of cervix cancer. The

*Read at a meeting of the New York Obstetrical Society, March 3, 1937.

metrium by methods generally used is inadequate. This is further brought out in studies recently completed by one of us⁵ in which the minimum dose of effective radiation delivered to the tumor in a large series of cases was calculated. The figures obtained when compared with the five-year survivals indicated that any method of therapy which delivers less than 3 erythema doses to a point 5 cm. lateral to the cervix will fail to control the disease in the majority of patients whom we now treat.

Reactions following this increased dosage of roentgen therapy were variable. Some patients suffered from a mild cystitis or proctitis which usually responded promptly to suitable therapeutic measures. The patients are observed regularly at follow-up clinic; the cervix is seen gradually to heal. The tumor sloughs away leaving a granulating surface. The infection then subsides and in time the cervix epithelizes over.

It should be noted that in some cases resistant foci of disease which have not regressed under the method outlined require interstitial radiation. We prefer the gold filtered radon seeds for this purpose. Interstitial radiation however, is not regarded favorably by us as a part of the primary treatment of cervical cancer. We do not believe it wise to use interstitial radiation in the presence of bulky, grossly infected lesions. The dose required is frequently so great that large ulcerating craters are left which frequently never heal. On the other hand, small doses of interstitial radium may be used to great advantage after the bulk of the tumor has disappeared and the lesion is clean. It has been our practice to repeat the cycle of roentgen radiation within four months. Since some patients such as the very obese are unable to receive the advantage of the roentgen cycle, we have to depend on radium therapy alone. Other cases, such as the very advanced, have to be treated palliatively by x-ray alone in order to avoid too great a tissue destruction by radium. Occasionally one of these patients surprises us and remains well over five years. Most of them however, are in such poor general condition on admission that they do not tolerate vigorous treatment, and we have to be satisfied with some amelioration of their symptoms of pain, bleeding, and discharge.

Patients of the more favorable group are treated vigorously in the hope of obtaining a "cure." Their initial treatment is never planned on the basis of the pathologist's report of the grade of the tumor or his conception of its radiosensitivity. This indication from the pathologist, while often of great value in the prognosis, is never allowed to influence our program of attempting to deliver a lethal dose to the tumor.

In view of the fact that histologic studies by Stewart and Arneson⁴ indicate that regressive phenomena are variable during the roentgen

We consider this method of cross-firing of the parametrium to be of extreme importance. Within a week or ten days a radium treatment of 1500 mc. hr. was given directly against the cervix by means of a vaginal applicator called the "bomb." This applicator could also be directed in such a way as to irradiate either or both fornices in a similar manner. The following day an intracervical and intrauterine application of 3000 mc. hr. was given. This form of applicator consisted of two radium capsules of unequal strength arranged in tandem within a rubber tube which was inserted into the cervical and uterine canal. The lower capsule was twice the strength of the upper one. In cases having bulky papillary and pedunculated lesions, the snare cautery was used to remove excess disease before the radium application. Antiseptic douches administered daily greatly aid in clearing up the infection and reducing the foul vaginal discharge. These douches also aid in preparing the site of disease for the application of the radium.

Since 1933, we have used the divided dose method of roentgen therapy while the radium applications have remained the same. By this method we have increased the dose to the parametria from 1 to 2.5 erythemas. This has been made possible by the addition of the two lateral pelvic fields and an increase of the total dose. The filter has remained the same but the target skin distance has been increased to 70 cm. Instead of the 750 r. dose per portal which we formerly gave at one treatment, we now treat two opposite portals daily with doses of 200 to 250 r. A total of 1500 r. per portal can be tolerated without permanent skin damage if given over a period of twenty-one days.

These changes in methods of therapy have paralleled increased knowledge concerning depth doses, distribution of radiation, and tissue tolerance. Laboratory and clinical studies have increased our knowledge as to the amount of radiation required to destroy the tumor. At the same time methods have been devised to protect the neighboring normal structures, viz., the bladder and rectum. Arneson and Quimby³ have published data concerning the distribution of radiation throughout the average-sized female pelvis for different physical factors of radiation. Their charts indicate clearly the advantage of the six field technique used by us now over the four field technique previously used and especially over the single large anterior and posterior fields used by some in external radiation. This advantage consists of increasing the amount of effective radiation to the parametrium without giving a corresponding increase to other noninvolved structures. This is accomplished by means of multiple small ports. Arneson and Stewart⁴ by means of serial biopsies taken during the course of external radiation, have shown that clinical regression and histologic changes parallel the dose given. They call attention to the necessity of delivering a larger dose of external radiation to the parametrium if any advance is to be made in the cure of cervical carcinoma. The amount of radiation delivered to the para-

This report then is based on 551 histologically proved cases of primary carcinoma of the cervix treated at the Memorial Hospital during a four-year period (see Table II).

TABLE II. SOURCE OF MATERIAL

Total cases seen	700*	Total primary cases	626
Primary	626	Not treated	34
Recurrent	51	No biopsy	41
Prophylactic	23	Basis this report	551

*One case of myosarcoma of the cervix treated but lost after 1½ years. It is not included because of reasonable doubt as to primary origin.

In studying these cases it becomes evident that several factors influence the prognosis for palliation or ultimate "cure." They are found to be (1) the clinical stage of the disease when treatment is instituted; (2) gross anatomy of the lesion and its latent period; (3) the age of the patient; (4) histology of the lesion; (5) the necessity of retreatments, and (6) previous operative procedures.

It has been pointed out that the percentage of early or favorable cases has not increased to any notable extent. We find that the clinical stage of the disease present when treatment is instituted is the most important factor in affecting the prognosis of a case of carcinoma of the cervix. It is remarkable that over two-thirds (70.2 per cent) of the patients in this series are either advanced or hopeless when admitted to the clinic. However, this figure is a slight improvement over the 75 per cent advanced cases previously reported by Healy.⁶ While the delay in establishing a correct diagnosis may in some cases result from ignorance or carelessness on the part of the physician, it is usually due to the failure of the patient to heed signs which should send her to the doctor. Association of irregular vaginal bleeding with the onset of the approaching menopause probably accounts for some of the delay. Chronic vaginal discharge, present over a period of years, may cause her to fail to notice its gradual increase or its blood-tinged nature until a frank hemorrhage occurs. The disease is then frequently quite advanced.

In classifying the cases as to clinical stage of disease we use the League of Nations system. We vary from it only in that we use the descriptive terms, *early*, *borderline*, *advanced*, and *palliative* instead of Groups 1, 2, 3, and 4. The criteria are essentially the same.

LEAGUE OF NATIONS CLASSIFICATION

Definition of Stages:

- Group 1: The growth is strictly limited to the cervix uteri. Uterus mobile.
- Group 2: Lesion spreading into one or more fornices with or without infiltration of the parametrium adjacent to the uterus, the uterus retaining some degree of mobility.
- Group 3: (a) Nodular infiltration of the parametria, on one or both sides extending to the wall of the pelvis, with limited mobility of the uterus or massive infiltration of one parametrium with fixation of the uterus.

cycle and that in some cases these changes were observed to cease toward the end of the treatment and shortly thereafter take on renewed activity, the question of whether tumors may become more radioresistant under therapy has been raised. Of this there is no actual proof; however, on the basis of the above observation, we have increased the daily dose of roentgen radiation toward the end of the cycle. In other words we have attempted to hit the lesion a little harder at the time when it is presumably more radioresistant. Thus, of late, we have used doses of 200 r. to two opposite portals daily until 1000 r. have been delivered to each of the six portals. Then the dose is increased to 250 r. for the remainder of the cycle, i.e., a total of 1500 r. per portal. This method has not been in use long enough for us to give any positive statement as to its value.

Source of Material.—This report is based on cases of carcinoma of the cervix treated on the Gynecological Service of the Memorial Hospital during the years 1928 to 1931 inclusive. These patients have been followed five to eight years. Seven hundred patients were seen. Of these, 626 were primary cervix cases, 51 were recurrent, and 23 were postoperative cases. These statistics are based on the primary cases so the other groups are omitted. Forty-one of the primary cases were eliminated because of lack of confirmatory histologic studies. The majority of them were biopsied elsewhere at the time of cauterization or tracheloplasty for lesions considered as inflammatory and only after the biopsy report of "suspicious of carcinoma" is returned are they referred to us. Because of these preliminary procedures we frequently are unable to obtain a subsequent positive biopsy, and therefore are obliged to treat such cases as carcinoma on the original report. Occasionally a biopsy report is lost. Statistics based on cases without histologic proof always raise questions of doubt and are to be avoided.

Thirty-four patients were not treated, some because of the advanced and extremely hopeless nature of their disease, others because of their failure to return when directed to do so. It may be stated that few cases are rejected because of advanced disease. We have found that some degree of palliation may be achieved in almost every case. However, those showing severe anemia, great loss of weight and weakness, or distant metastasis suggest a hopeless prognosis. They have to be referred elsewhere for terminal care.

The absolute cure rate is not used in reporting our results as it is based on the total cases seen whether treated or not. Cases partially or even adequately treated in other institutions (and appearing in their figures) and later on coming under our observation for further care should not also appear in figures indicating our cure rate. Absolute figures are not indicative of the value of any particular method of therapy. Their only value is to indicate the volume of cases passing through the clinic.

He points out the difficulties of such an estimation due to the individual peculiarities of the different types of carcinoma. Difference in growth rate, trauma, inflammation, and the effect of pregnancy add to the difficulties. The conclusion as to the necessity of frequent pelvic examination is obvious.

Recently in an effort to shed more light on this latent period of growth, we questioned closely a group of new patients concerning the length of time symptoms existed before seeking medical advice. This interval varied from three weeks to three years with an average of 10.4 months. If cancer of the uterine cervix can remain for such long periods of time without causing sufficient symptoms to bring the patient to her doctor, it is small wonder that such large numbers are advanced when first examined in the clinic. Recently this was excellently demonstrated by a case under our observation.

Case Report.—M. O. This patient, a fifty-seven-year-old female was referred to the Memorial Hospital with a diagnosis of carcinoma of the cervix. Her lesion had been discovered during a routine examination. There were no symptoms. Biopsy taken from a small ulceration of the cervix had been diagnosed as carcinoma and confirmed by Dr. Stewart. When she presented herself at our clinic, the cervix was perfectly normal with no evidence of disease. Further biopsies by us failed to confirm the diagnosis of cancer. Such a case would ordinarily be treated in the routine way. This one was not but instead remained under our close observation. After three years of observation and during which time symptoms never occurred, the cervix was noted to be increasing in size. Biopsy taken at that time showed epidermoid carcinoma Grade II. There was no evidence of parametrial involvement and as far as could be determined the case was still clinically early. Treatment was promptly instituted.

This case was undoubtedly neglected. It illustrates, however, a long latent period in the development of carcinoma of the cervix.

The age of the patient unquestionably affects the prognosis as is shown in Table V. The age was recorded in 539 cases. The youngest and oldest were twenty-four and seventy-four years, respectively.

TABLE V. AGE GROUPS—FIVE-YEAR SURVIVALS

AGE	CASES		5-YEAR SURVIVALS	
	NO.	PER CENT	NO.	PER CENT
20-29 yr.	12	2.2	0	0
30-39 yr.	85	15.7	32	37.6
40-49 yr.	159	29.5	37	23.2
50-59 yr.	183	33.9	59	32.2
Over 60 yr.	100	18.5	22	22.0

The greatest concentration of cases occurs during the menopausal and postmenopausal years. This is in accordance with figures of other observers. There is, however, an appreciable number of cases falling in the younger age groups. The very young and the aged did poorly. Study of these figures would suggest that women developing cervical cancer in the fifth decade probably tend to ignore the occurrence of

- (b) More or less superficial infiltration of a large part of the vagina, with a mobile uterus.
- (c) Isolated metastases in the pelvic glands, with a relatively small primary growth.
- (d) Isolated metastases in the lower part of the vagina.

Generally speaking all cases not falling into Groups 2 or 4 will be placed under Group 3.

- Group 4:
- a. Cases with massive infiltration of both parametria extending to the walls of the pelvis.
 - b. Carcinoma involving the bladder or rectum.
 - c. The whole vagina infiltrated (rigid vaginal passage) or one vaginal wall infiltrated along its whole length with fixation of the primary growth.
 - d. Remote metastases.

We find this grouping more satisfactory than that of Schmidt. Rarely do we see a case early enough to call it Schmidt Class I. Table III indicates the grouping of this series of cases. The number and percentage of cases in each group with their five-year survival rate is indicated.

TABLE III. CARCINOMA OF THE CERVIX

CLINICAL GROUPS		FIVE-YEAR SURVIVALS			
LEAGUE OF NATIONS GROUPS	CLINICAL CLASS	NO. CASES	PER CENT TOTAL	LIVED 5 OR MORE YEARS	
				NUMBER	PER CENT
1	Early	86	15.5	50	58.1
2	Borderline	78	14.2	20	38.4
3	Advanced	308	55.9	68	22.0
4	Palliative	79	14.4	5	6.3
Total		551	100.0	153	27.7

Cases lost to follow-up or dead of intercurrent disease are considered as dead of cancer. Twenty-eight cases or 5 per cent were lost to follow-up.

Gross anatomic types of lesions with their different growth factors influence the prognosis. This is evident when it is seen that the so-called latent or silent period of growth is different for the different types. The infiltrative lesion is more likely to have a longer silent period of development than either the ulcerative or proliferative types. We are of the opinion that in some instances, cancer of the cervix may develop without symptoms over a period of months. Actually, we are without much knowledge concerning this silent period in the development of cervical carcinoma. Various estimates have been made but in general it is thought to be limited to a few months. Goecke⁷ in a study of 228 cases found the average symptom period and symptom-free period as follows:

TABLE IV

SYMPTOM PERIOD		SYMPTOM-FREE PERIOD	
Group I	3 mo.	1 mo.	
Group II	3.5 mo.	1.8 mo.	
Group III	6.9 mo.	4.0 mo.	
Group IV	10.5 mo.	6.5 mo.	

the majority of observers were of the opinion that the adenocarcinomas of the cervix were radioresistant. Our experience⁶ and that of others would indicate that this is not true.

Regardless of the radiosensitivity of the different types of lesion, the curability as measured by the five-year survivals does not differ widely for the different groups. The distribution of the cases among the groups is about what we would expect. The number of adenocarcinomas is small and the high survival rate may be entirely accidental. We can say then with a fair degree of accuracy that the cell type or grade of the lesion is apparently not of such prognostic importance as far as the five-year cure rate is concerned in the radiation treatment of cervix cancer, but is of extreme importance if surgery is contemplated.

Retreatments.—Another factor affecting the prognosis is that of retreatments. Patients who receive the full course of therapy including the preliminary cycle of roentgen radiation, vaginal and intrauterine radium application, and followed by the second roentgen cycle seldom require retreatment if they are to do well over a period of years. This course of therapy as given in the cases reported here requires three to four months to complete. However, resistant foci of disease occasionally require interstitial therapy by implantation of gold filtered radon seeds. Patients too obese to tolerate external radiation may require additional applications (direct) of radium. It is interesting to note that of the 153 patients in this series reported as surviving five or more years, only 14 or 9.1 per cent were ever retreated after the original planned course of therapy was carried out. This corresponds with our experience previously published.⁶

Formerly, considerable emphasis was placed on the questionable prognosis in carcinoma developing in the cervical stump. The so-called stump carcinomas are considered as primary cervix carcinomas as long as the histology is consistent with cervical origin. If the lesion is identified within the year following the supracervical hysterectomy, we believe that it is reasonable to assume that it was present and unrecognized at the time of the operation. Such cases can be classed as primary cervix carcinomas but cannot be regarded as having arisen in the stump subsequent to operation. In this series of cases, the discovery of the lesion was preceded by operation by from four to thirty years. Thirteen stump cases were seen giving an incidence of 2.3 per cent.

TABLE VII. INCIDENCE AND PROGNOSIS—CARCINOMA CERVICAL STUMP

AUTHOR	NO. CERVIX CASES	NO. STUMP CASES	INCIDENCE	5-YEAR SURVIVAL
Scheffey ¹¹	273	10	3.66%	42.4%
Sackett ¹²	664	50	7.5%	48.4%
Meigs ¹⁴	1218	26	2.1%	7.6% (4 yr.)
Healy-Arnson ¹²	2600	67	2.6%	14.0%
Healy-Frazell	557	13	2.3%	53.8%

bleeding at unexpected times and to attribute it to the menopause. They thereby delay seeking medical advice until the disease is well established. In the younger women as well as those in the postmenopausal group, such irregular bleeding is more likely to receive prompt investigation, thus leading to earlier diagnosis with improved prognosis. Our experience would indicate that the prognosis is very poor under the age of thirty. This is, of course, in accord with the poor prognosis of malignant disease in the early years of life.

An effort was made to determine whether the histologic grade of the tumor or its classification as to cell type and radiosensitivity affected the five-year results. In this series, the pathologist was able to grade and determine the cell type in 537 out of the 551 cases. This classification was based on the degree of differentiation of the cells. *Grade I* is the adult, ripe, or spinal cell type showing squamous cells well differentiated and frequently containing pearls. *Grade II* is less differentiated but intermediate between the first and third groups. It is known as the mid-ripe, plexiform, or transitional cell type. *Grade III* is the unripe, spindle, or anaplastic cell type. The adenocarcinomas form a small but distinct group. This classification is in accord with that of Chambers⁸ who classified a large number of cases using an elaborate and detailed system but concluded that the three main groups were all that were essential.

TABLE VI. HISTOLOGIC TYPES

	CASES		LIVED 5 YEARS	
	NO.	PER CENT	NO.	PER CENT
Ripe (adult)	88	16.3	26	29.5
Mid-ripe (transitional)	351	65.3	88	25.0
Unripe (anaplastic)	82	15.2	20	24.3
Adenocarcinoma	16	2.9	6	37.5

There has been considerable divergence of opinion concerning the radiosensitivity of the various groups. Stewart⁹ has pointed out the difficulties encountered in making such a study and the dangers of making any positive statement on clinical observations alone. He quotes Lacassagne as believing that the various types show small differences in their response to radiation. Healy and Cutler¹⁰ have stated that the radiosensitivity increases with the degree of anaplasia and concluded that the combination of the degree of malignancy and radiosensitivity was of considerable prognostic significance as regards cure, depending upon whether radiation or surgery was the method of treatment. They emphasized that the surgical end-results became progressively poorer as the malignant qualities of the tumor cells increased. Whereas with radiation therapy the increasing malignant quality of the tumor cells seemed to be largely compensated for by increased radiation sensitivity, so that the end-results remained the same for all cell types. Formerly

A few patients develop pelvic peritonitis following radiation treatment. This is usually due to a reactivation of an old pelvic inflammatory condition. Such cases usually do badly. Cases developing septicemia following intrauterine radiation are rare.

Fistulas developing as a complication of carcinoma of the cervix are serious; they may be vesicovaginal, rectovaginal, or a combination of the two varieties, and are usually a manifestation of advanced disease rather than excessive radiation. Smith¹⁶ found in a recent study of this subject that the incidence of fistulas was twice as great in the untreated as in the treated cases. He concluded that in patients treated by radiation methods the incidence was increased by interstitial radiation, lack of filtration, retreatments, infection, structural type of the lesion and hysterectomy before irradiation.

The appearance of distant glandular metastasis to the groin, neck, and supraclavicular nodes is somewhat unusual. Chest and bone metastases are rather rare occurrences.

Jacox¹⁷ and his associates have recently published an account of what in this country was a relatively unknown complication following pelvic irradiation. This is the spontaneous fracture of the neck of the femur following irradiation of the pelvis for different forms of malignant disease of the female pelvic organs. These fractures were spontaneous without evidence of trauma, and in none of these cases could metastatic bone lesions be detected. The bones show a moderate amount of osteoporosis which is undoubtedly due to some devitalization effect of the radiation. They found 14 cases of fracture of which three were bilateral. We have recently encountered two cases of spontaneous fracture of the femur following radiation for malignant lesions in the pelvis. In one of these cases, the primary lesion was in the corpus, recurrent now in the cervix seven years following supracervical hysterectomy for a supposed benign condition.

CASE REPORTS

CASE 1.—D. H. The patient was fifty-seven years old when she was referred to the Memorial Hospital in May, 1932, with a diagnosis of carcinoma of the cervix. The biopsy indicated that the lesion was corpus in origin. A supracervical hysterectomy had been done seven years previously for a supposed benign condition. A preliminary roentgen cycle consisting of 750 r. to each of 4 pelvic fields by the usual technique in use at that time was given. In May, 1932, she was treated by means of the radium bomb against the cervix for 1,509 mc. hr. Following this a single capsule of radon was placed in the cervical stump for 1,500 mc. hr. The second roentgen cycle was given within four months, the factors used being the same as before. The patient showed excellent regression and remained without clinical evidence of disease until December of 1936. In the interim, i.e., January, 1936, she complained of pain in the right thigh. X-ray films of the bones were negative for evidence of metastasis. Fifteen days later she suffered a spontaneous fracture of the right femur. Further films failed to show evidence of metastasis to bone.

We are inclined to agree with other writers on the subject that the incidence is so low that supracervical hysterectomy is adequate for benign lesions of the corpus in the presence of an apparently normal cervix. The five-year salvage for the group seen was 53.8 per cent and is somewhat surprisingly high in view of the difficulties encountered in the proper application of the radium. (Table VII gives results reported by others.)

Complications.—These may be early or late following radiation for carcinoma of the cervix. They may be mild or severe and due to the treatment or to the disease itself. Early complications are usually mild and consist of radiation proctitis or cystitis which runs a rather mild course and responds to symptomatic treatment.

Late radiation changes in the bladder have received considerable attention. They vary from congestion to actual ulceration of the bladder mucosa. The resulting cystitis is frequently severe and may last a long time. It is often complicated by calcific deposits. These changes are thought to be due to radiation endarteritis which requires from one to two years to develop. It is, of course, of prime importance to distinguish between inflammatory changes and actual neoplastic invasion of the bladder before therapy is instituted. Dean¹⁵ has made an extensive study of this condition and reports that at least 2 per cent of the cases of carcinoma of the cervix which we treat develop bladder complications.

Radiation proctitis is similar to the changes noted in the bladder. It manifests itself by bloody mucus, diarrhea, and severe rectal pain. Ulceration of the anterior rectal wall will usually be found and perforation may occur or rectal stricture may develop and cause obstruction. In this series, stricture was seen 9 times and was severe enough to require operative interference in 3 instances.

Pyometra of greater or lesser degree is fairly common. It occurs in retroverted uteri where drainage is poor and in those in which the cervical canal becomes obstructed by tumor or radiation changes. Dilatation of the cervical canal and irrigations of the uterine cavity may clear up the condition but often hysterectomy is required.

TABLE VIII. COMPLICATIONS

Pyometra	17*
Fistulas	
Rectovaginal	9
Vesicovaginal	18
Combined	2
Rectal stricture	9
Distant metastasis	
Groin, neck, supraclavicular nodes	6
Chest	3
Spine	3

*Pyometra probably was much more common than the chart indicates. The number indicates the cases which required either hysterectomy or prolonged drainage.

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AN ANALYSIS OF THREE HUNDRED CONSECUTIVE CASES OF PRIMARY CERVICAL REPAIR*

GLENN A. WOOD, M.D., SYRACUSE, N. Y.

(From the Department of Obstetrics, Syracuse General Hospital)

SINCE early 1929, it has been my routine practice, after completion of the third stage of labor, to inspect and primarily repair lacerations of the cervix that may be observed. In November, 1929, I reported¹ my experience with 50 cases of primary cervical repair. This previously reported series is included in this report, but as the nature of the report is of a different character, I feel justified with its inclusion.

The following were the objectives of study in this series of cases:

1. Is cervical laceration a common observation after completion of the third stage of delivery?

To secure this series of 300 consecutive cases of primary cervical repair, it was necessary to include 341 consecutive deliveries. The incidence of cervical laceration was 88 per cent.

I am mindful of the fact that this is considerably higher than that recorded by others. I am unable to explain this apparent discrepancy. To me, the 88 per cent more nearly approximates the number of women who show cervical lacerations and the pathology resulting from those lacerations at the postpartum examination.

We must conclude, however, that laceration of the cervix after completion of the third stage of delivery is fairly common.

2. Can present teaching of dilatation and, especially, retraction of the cervix during the first stage of labor be correlated with the observed length of the vaginal portion of the cervix after completion of the third stage, when the cervix is observed for primary repair?

*Read before the Onondaga Medical Society, January 5, 1937.

CASE 2.—M. C., aged fifty-six years, white female, was referred to the Memorial Hospital June 12, 1934, with a diagnosis of carcinoma of the cervix. The lesion was advanced. Biopsy was reported as plexiform epidermoid carcinoma Grade II. Divided dose roentgen therapy was given. Six pelvic portals were used and the daily dose to two opposite fields was 300 r. A total of 1,800 r. per portal was given. One month later radium was inserted into the cervix and corpus for 3,000 mc. hr. A fair amount of regression was obtained. Seven months later a second roentgen cycle was given with the same factors as the first one except that a total of 1,500 r. per field was given. The lesion cleared up, and when the patient was lost track of in July, 1935, there was no clinical evidence of disease. X-ray films of the pelvis and femora in September, 1936, failed to show evidence of fracture or metastatic disease. A moderate degree of osteoarthritis was noted. Jan. 10, 1937 the patient returned to the clinic complaining of pain in the left hip and difficulty in walking. X-ray films of the pelvis showed fracture of the neck of the left femur without evidence of bone metastasis.

The occurrence of these two unusual complications is of interest in view of the fact that it had not previously been encountered by us in the radiation treatment of over 3,000 patients with malignant disease of the pelvis and in all of whom a careful follow-up record has been maintained. We cannot believe that it will occur often enough to be of serious importance in this form of therapy.

SUMMARY

Five hundred and fifty-one cases of histologically proved primary carcinoma of the cervix treated at the Memorial Hospital during the years 1928 to 1931 inclusive were used as a basis for this statistical study. Analysis of these cases shows:

1. The salvage as measured by the five-year survival rate is improving but is still far from satisfactory.
2. Further improvement of these results is dependent upon earlier diagnosis. Seventy per cent of the patients seen in this series were either advanced or hopelessly ill on admission. This is a reduction of 5 per cent in the total number of advanced cases.
3. Because of the long silent period of growth many cases will not be diagnosed until late unless more frequent pelvic examinations are made.
4. The dose of effective radiation delivered to points 3 cm. or more lateral to the cervical canal is inadequate to control the disease in 70 per cent of the cases.
5. Changes in technique are directed toward increasing the dose to the parametria without destruction of normal structures.
6. The prognosis is influenced by the clinical stage of the disease, age of patient and the dosage of therapy given.
7. The importance of preliminary roentgen radiation is stressed.
8. Important complications are noted.

position. By this theory, the cervix is not, at least, entirely retracted into the lower segment and its appearance and situation would correspond to that as observed when primary repair is done.

3. Is one side of the cervix more commonly and more deeply lacerated than the other?

Using the classification of observed lacerations as explained under objective 2, I have prepared Table I to show the site of the lacerations, the number of cases, with percentages, and the extent of the lacerations as to numbers and percentages.

TABLE I. SITE AND DEPTH OF LACERATIONS

	TOTAL NO. CASES		SMALL		MODERATE		EXTENSIVE	
	NO.	%	NO.	%	NO.	%	NO.	%
Right side	86	28.4	4	4.3	23	26.8	59	68.9
Left side	136	45.4	6	4.4	79	58.0	51	37.6
Equal, right and left sides	66	22.1	0	0	41	62.1	25	37.9
Posterior lip	12	4.1	0	0	4	33.3	8	66.6

In this series the left-sided cervical tears exceeded the right by about 17 per cent. This finding seems to agree with that of other observers. There were 22.1 per cent of the patients who showed an equal tear of both sides and 4.1 per cent showed a laceration of the posterior lip. The finding of equal right and left side and posterior lip lacerations does not seem to be especially emphasized in obstetric literature. The moderate size tears were common to the left cervix while the extensive were more common to the right cervix. The posterior lip lacerations were quite decidedly extensive.

4. Does forceps application or a version increase the risk of a cervical tear?

Table II lists the types of forceps applications that were made. For both forceps and version it lists the number of cases and the number and percentage of the extent of the lacerations of the cervix that were observed.

TABLE II. FORCEPS AND VERSION

	NO. CASES	SMALL		MODERATE		EXTENSIVE	
		NO.	%	NO.	%	NO.	%
Low forceps	39	2	5.1	24	61.5	13	33.4
Midpelvic forceps	1	-	-	1	100.0	-	-
Axis-traction	1	-	-	-	-	1	100.0
Bill-Scanzoni	17	-	-	8	47.0	9	53.0
Versions	7	-	-	4	57.1	3	42.9

Because of the small number of patients (58) in whom forceps were applied, definite conclusions as to the rôle that forceps application plays in the production of a cervical tear cannot be drawn. However, in this series the 39 low forceps applications produced a greater percentage

I have classified the observed lacerations in this series as: small if the laceration was $\frac{1}{2}$ to 1 inch in length, moderate, if from 1 to 2 inches, and extensive if 2 inches or over.

In visualizing a cervix immediately after delivery, it might seem to many that an observed laceration of the cervix of 2 inches or over would be of sufficient length to invade the broad ligaments or the lower uterine segment. Such is not the case.

I am unable to correlate present-day teaching of retraction of the cervix during the first stage of labor with the observed length of the vaginal portion of the cervix after completion of the third stage, when the cervix is observed for primary repair. My experience with this series has demonstrated that immediately after the third stage there is visible vaginally about 2 inches of edematous cervix anteriorly, and from 3 to 4 inches laterally and posteriorly. The posterior section, at least, is usually well thinned out:

There is no definite statement in obstetric textbooks as to the length of the vaginal portion of the cervix after completion of the third stage. One is given the impression that there is complete retraction of the cervix into the lower uterine segment, that is, there is no vaginal portion remaining. For example, DeLee in his textbook² states, "Coincident with the dilatation, the cervix is drawn up into the abdomen, so that when the dilatation is complete, the external os is high, almost out of reach of the finger." Williams³ and Beek,⁴ also, express this view.

If the cervix during the first stage is retracted so that its vaginal portion is short or absent, as is so clearly demonstrated in textbook drawings and text, how are we to explain its appearance as a distinct portio vaginalis at the completion of the third stage when it is exposed for lacerations?

One possible explanation might be to admit effacement as described, partially to explain dilatation by a contraction of longitudinal fibers of the uterus which are inserted into the distal part of the cervix and which act to open the external os, much as the iris diaphragm of a microscope opens, likewise to admit that the forces of labor during the first and second stages cause the "passenger" to exert a force downward and outward which aids in dilatation. These forces cause the posterior and lateral cervix to thin out and lengthen due to its approximation against a resistant vaginal wall and pelvic floor. The anterior cervix is, also, lengthened during flexion, descent and internal rotation of the first and second stages. After the first stage is complete the cervix can and does slip over the head. When extension begins, the head, neck, shoulders, and body, in turn, are firmly pressed against the under part of the symphysis which pressure does not permit the anterior cervix to advance further. It is held back of the symphysis by this upward fetal pressure during extension, thus explaining its retrosymphysial

b. *Parity*: Table IV lists the number of patients in each parity group, also, the percentages of the extent of the cervical lacerations observed in the different parity groups.

TABLE IV. PARITY COMPARISON

PARITY	NO. PATIENTS	PER CENT SMALL	PER CENT MODERATE	PER CENT EXTENSIVE
1	108	7	54	39
2	84	5	62	33
3	62	2	50	48
4	25	12	52	36
5	9	11	55	34
6	4	-	50	50
7	3	-	66	34
8	3	-	34	66
10	1	-	-	100
11	1	100	-	-

The greatest percentage of moderate lacerations occurred with parities ii and vii. The largest percentage of extensive lacerations occurred with parity viii. We can draw no definite conclusions from these statistics, unless it be that cervical laceration is common to any parity.

c. *Weight of Baby*: There were 302 babies to consider in this review, as twin births occurred twice. Table V shows the number of babies that were found in the various weight groups as well as the percentages of small, moderate, and extensive lacerations that were observed in these different weight groups. The weights are expressed in pounds and ounces.

TABLE V. WEIGHT OF BABY FACTOR

WEIGHT GROUP	NO. BABIES	PER CENT SMALL	PER CENT MODERATE	PER CENT EXTENSIVE
-6	37	0	67.5	32.5
6 ¹ -7 ⁸	127	4.7	58.2	37.1
7 ⁹ -8 ⁸	98	4.1	57.1	38.8
8 ⁹ +	40	5.0	22.5	72.5

There is a steady increase of extensive lacerations with the increased weight of the baby. We conclude, therefore, that the larger the baby the more extensive the laceration.

d. *Presentation and Position*: Because of the two sets of twins there are 302 primary presentations and positions to consider. It is quite impossible to say which of the two positions of the twins produced the cervical tear. I have chosen what appeared to be the more unusual position and presentation. Due to the close association that the use of forceps necessitated in delivering some of these babies, I have, again, included forceps subdivisions.

Table VI gives the number of cases found under each presentation and position, the type of forceps application to the position, and, also, the percentage of small, moderate and extensive lacerations observed under the several presentations and positions.

of moderate lacerations than did spontaneous deliveries (average 52 per cent) as shown in Table VI. The 17 Bill-Scaanzoni maneuvers produced a greater percentage of extensive lacerations than did spontaneous deliveries (average 43 per cent) as shown in Table VI. The 7 versions showed a high percentage of both moderate and extensive lacerations:

5. Is cervical laceration more often observed in primiparas or multiparas?

In this series there were 108 primiparas and 192 multiparas who received primary repairs. In the total number of cases, 341, from which this series was taken, there were 119 primiparas and 222 multiparas. There were, therefore, 90.7 per cent of primiparas who were repaired and 86.4 per cent of the multiparas. This percentage shows no great difference. The cervical laceration is common to both primiparas and multiparas.

6. Is hemorrhage from the cervical tear a common observation?

In this series not once have I felt that bleeding from the torn edges of the cervix was of sufficient intensity to demand a repair. I was, perhaps, fortunate in this series not to encounter a hemorrhage from the lacerated cervix. This complication must always be considered in vaginal bleeding after the third stage with a firm fundus. We must, however, conclude that hemorrhage from a lacerated cervix is not a common observation.

7. Are any of the following factors present which will tend to produce a cervical tear: Age of patient, parity, weight of baby, presentation and position, premature rupture of the membranes, hours in the first and second stages of labor, and a large bisachromial diameter of the baby?

a. *Age of Patient.*—Table III not only gives the number of patients that fell in the different age groups, but also, the percentage comparison of the extent of the lacerations in these different age groups.

TABLE III. AGE COMPARISON

AGE GROUP	NO. PATIENTS	PER CENT SMALL	PER CENT MODERATE	PER CENT EXTENSIVE
14-19	21	4.7	52.3	42.8
20-25	101	3.0	55.4	40.5
26-30	95	4.2	54.7	41.0
31-35	43	2.3	46.5	51.1
36+	40	7.5	47.5	45.0

There seems to be no age group to which cervical laceration with labor is distinctly common. In this series there were more small tears in the age group of 36+. There were more moderate tears in the age group twenty to twenty-five. There were more extensive tears in the age group thirty-one to thirty-five. These differences are not distinctive. We must conclude therefore, that the cervical laceration is common to all ages.

f. *Hours in First and Second Stages of Labor:* Here I have considered two factors, an excessively long and an excessively short labor. What constitutes an excessively long or an especially short labor? Here, again, personal opinion enters. I have subdivided the cases into primiparas with a first and second stage of over eighteen hours as a long labor and labor under nine hours as a short labor. Multiparas in labor over twelve hours I have classed as a long labor and under six hours as a short labor.

Table VII gives the number of cases under each of these subdivisions and also the percentages of the small, moderate, and extensive lacerations that were observed.

TABLE VII. HOURS IN FIRST AND SECOND STAGES OF LABOR

	NO. CASES	PER CENT SMALL	PER CENT MODERATE	PER CENT EXTENSIVE
Primiparas Over 18 hr.	32	15.6	46.8	37.5
Primiparas Under 9 hr.	28	7.1	53.5	39.4
Multiparas Over 12 hr.	49	6.1	40.8	51.0
Multiparas Under 6 hr.	77	3.8	57.1	39.1

Primiparas in labor over eighteen hours show a marked increase in the percentage of small lacerations and also the smallest percentage of extensive lacerations. Multiparas in labor over twelve hours show a great increase in the percentage of extensive lacerations. Multiparas in labor under six hours show quite an increase in percentage of moderate lacerations. These observations are not conclusive.

g. *Bisachromial Diameter of the Baby:* In this series of cases the bisachromial diameter was measured 246 times. Table VIII gives the number of babies observed with the bisachromial diameter of 12 cm. or over, the number of babies with less than 12 cm., also, the percentages of the extent of the lacerations of the cervix observed.

TABLE VIII. BISACHROMIAL DIAMETERS OF BABIES

	NO. BABIES	PER CENT SMALL	PER CENT MODERATE	PER CENT EXTENSIVE
12 cm. or over	154	1.2	35.0	63.8
Less than 12 cm.	92	4.3	78.2	17.5

In this series there is a marked increase in the percentage of extensive lacerations with babies with a bisachromial diameter of over 12 cm. In my previous report, it was then my contention that this diameter of the "passenger" was more responsible than any one factor in the production of the cervical tear. These statistics seem to bear out that contention. This factor is, of course, closely associated with the weight factor as shown in Table V.

The difference is not remarkable in the percentage of extensive tears occurring with spontaneous L.O.A. (line 1) and spontaneous R.O.A. (line 3). A smaller percentage of extensive tears occurred in both L.O.A. (line 2) and R.O.A. (line 4) when low forceps was applied. The

TABLE VI. PRESENTATION AND POSITION

	PRESENTATION AND POSITION	NO. CASES	PER CENT SMALL	PER CENT MODERATE	PER CENT EXTENSIVE
1	L.O.A. Spontaneous	134	4.4	53.0	42.6
2	L.O.A. Low forceps	24	8.3	58.3	33.4
3	R.O.A. Spontaneous	86	3.4	51.1	45.5
4	R.O.A. Low forceps	16	0	68.7	31.3
5	R.O.A. Ax. tract.	1	0	0	100.0
6	R.O.A. Midforceps	1	0	100.0	0
7	R.O.P. Spontaneous	3	33.3	33.3	33.3
8	R.O.P. Scanzoni	12	0	58.3	41.7
9	L.O.P. Scanzoni	5	0	20.0	80.0
10	R.M.A.	2	0	0	100.0
11	L.M.A.	3	0	66.6	33.3
12	R.S.A.	5	0	20.0	80.0
13	L.S.A.	7	14.3	71.4	14.3
14	R.S.P.	1	0	0	100.0

number of cases of face and breech presentation is, I feel, too small upon which to base any observations. A Bill-Scanzoni maneuver in R.O.P. (line 8) did not increase the incidence of extensive tears as compared with spontaneous R.O.A., but its use in L.O.P. shows a marked increase in extensive tears.

c. *Premature Rupture of the Membranes*: The definition that I have selected for this condition is, a rupture of the membranes before the completion of the first stage of labor. With a desire to conduct a labor with the minimum of examinations, it is usually impossible to state exactly when the second stage begins. I have felt that 66 of the 300 cases presented had a definite premature rupture of the membranes, the longest of which was thirty-seven hours before labor started. This patient, incidentally, showed a moderate laceration. The 66 patients showed 3 per cent small, 54.4 per cent moderate, and 42.5 per cent extensive cervical lacerations. The percentage of extensive lacerations in this series compares favorably with the extensive lacerations percentages of both spontaneous L.O.A. and R.O.A. as listed in Table VI. We must conclude, therefore, that premature rupture of the membranes was not a definite factor in this series in the production of a cervical tear.

My results have been listed as poor, fair, and excellent; poor, if on postpartum examination there was an area of erosion larger than 3 mm. on either or both lips of the cervix or, if any pathology should be present that would exceed this in amount; fair, if hair line erosion to 3 mm.; and excellent if no erosion was observed and the contour of the external os seemed to resemble that of a nulliparous cervix. Table IX shows the results taken collectively, in primiparas and in multiparas. It shows the number of cases in each group as well as the number and percentage of cases under the poor, fair, and excellent classifications. Finally, the table shows the number of cases and the percentage of those in each group that did not return for a postpartum examination.

TABLE IX. RESULTS

	NO. CASES	POOR		FAIR		EXCELLENT		NO EXAM. POSTPART.	
		NO.	%	NO.	%	NO.	%	NO.	%
Collectively	300	12	4	61	21	186	64	41	11
Primiparas	108	2	2	15	14	82	76	9	8
Multiparas	192	10	5	46	25	104	54	32	16

In this series a large majority of the patients were definitely benefited. Primiparas, especially, show a high percentage of excellent results. However, a certain percentage of women will not return for a postpartum examination.

11. Does a percentage comparison of the extent of the cervical pathology observed at the sixth-week examination in patients with and without a primary cervical repair, justify us in concluding that, with the primary repair there is a distinct lessening of observable cervical pathology?

Using the same standards of comparison as in Table IX, I have classified the results of postpartum observations in 150 patients who did not have a primary cervical repair. These results are recorded in Table X.

TABLE X. RESULTS—150 CASES WITHOUT PRIMARY CERVICAL REPAIR

	NO. CASES	POOR		FAIR		EXCELLENT	
		NO.	%	NO.	%	NO.	%
Collectively	150	108	72	34	22	8	6
Primiparas	33	23	69	7	21	3	10
Multiparas	117	89	76	20	17	8	7

Table XI gives a percentage comparison as to results on postpartum observations of the cervix in cases of primary cervical repair as in Table IX and those cases without primary repair as in Table X. Table IX shows that there were 11 per cent taken collectively, 8 per cent of primiparas and 16 per cent of multiparas, who had no postpartum examination. This explains the apparent discrepancy of percentage tabulations in the primary cervical repair group of Table XI.

8. Is there an added risk of infection when a primary cervical repair is done?

In this series of cases there was no mortality. There were 10 primiparas and 6 multiparas, that showed a morbidity according to the standard of a temperature of 100.4° F. during the patient's hospital stay, on any two successive days, not including the first day. This gives a morbidity of 5.3 per cent. I have carefully reviewed the 16 patients that showed a morbidity. With the possible exception of one case, I failed to discover any connection between the morbidity and the primary repair. Pyelitis, tonsillitis, and bronchopneumonia were assumed to be the causes of the morbidity. In all patients but one, as an indication of no pelvic infection, the fundus involuted in the usual time. It is my conclusion that primary repair of the cervix, if done with hospital equipment, does not add to the risk of infection.

9. Does a subsequent delivery predispose to as great or a greater cervical tear? Does cervical dystocia result from a previous repair?

In this series 53 patients were delivered two or more times and the cervix observed for lacerations. Forty-eight of these were delivered two times with the following results:

- 10 (18.6 per cent) showed extensive with first and an extensive with second.
- 4 (7.5 per cent) showed moderate with first and an extensive with second.
- 17 (32.0 per cent) showed moderate with first and a moderate with second.
- 4 (7.5 per cent) showed extensive with first and none with second.
- 12 (22.6 per cent) showed extensive with first and a moderate with second.
- 1 (1.8 per cent) showed none with first and a moderate with second.

Four patients were delivered three times:

- 2 (3.7 per cent) showed a moderate laceration with all three deliveries.
- 1 (1.8 per cent) showed extensive with first and second and a moderate with third.
- 1 (1.8 per cent) showed moderate with first and extensive with the next two.

One patient was delivered four times. There was an extensive with the first and a moderate with the next three deliveries.

Regarding cervical dystocia resulting from a previous repair as evidenced by an increase or decrease in hours of first and second stages of labor in cases that have been primarily repaired one or more times:

Thirty (56.6 per cent) patients showed a decrease. Twenty (37.7 per cent) showed an increase of from one-half hour to not over five hours and 3 (5.6 per cent) showed the same.

From these observations it is my conclusion that there is no special evidence to show that subsequent deliveries are predisposed to greater lacerations of the cervix nor that cervical dystocia results from a previous primary repair.

10. Is there complete elimination of subsequent cervical pathology with a primary cervical repair?

THE EFFECT OF PREGNANCY ON MALIGNANT TUMORS*

FRANK R. SMITH, M.D., F.A.C.S., NEW YORK, N. Y.

FOR many years authors have published reports of isolated cases of malignant tumors complicated by pregnancy, and in most instances the conclusions have been that the pregnancy had a harmful effect. Only rarely have authors taken the stand that pregnancy had any beneficial influence.

This confusion is evident in the following conflicting opinions:

Ewing¹ has stated that pregnancy has an unfavorable influence upon the course of many carcinomas, but that this influence is not always apparent. Neill² quotes Zweifel and Simpson as feeling that pregnancy activates growth in malignant tumors; Weibel,³ Wolfe, Meyer, Stöckel⁴ as convinced that pregnancy retards growth; and Hoffmeier, Kobak, and Cullen⁵ as finding pregnancy to have no effect on growth. Similarly, of 603 cases of pregnancy associated with malignant tumors collected by Sarwey,⁶ 43.3 per cent died at labor or in the puerperium, yet Weibel³ reported two-thirds of his patients having carcinoma of the cervix and also being pregnant as without recurrence in five years after hysterectomy. Williams⁷ states that in cases of pregnancy associated with carcinoma of the uterus, abortion occurs in 30 to 40 per cent of cases. Adair³⁰ has pointed out in patients with cancer of the breast that every third pregnancy resulted in an abortion, whereas in his control group abortion occurred only once in each 7 pregnancies. Lee,⁸ in reporting 306 patients with mammary cancers forty years of age or less, cites 11 patients complicated by pregnancy. Of 7 operable patients only 1 lived more than three years, and she died five years and ten months after operation. He concludes that when pregnancy complicates mammary cancer the outlook for that patient is bad, and that immediate therapeutic abortion should be done. The relationship of changes in the breast to ovarian function has been discussed by Abbe,⁹ Allen and Doisy,¹⁰ Bagg,¹¹ and others, and recently elaborated upon by Taylor.¹²

The increasing tendency of surgeons to advise x-ray castration of young women having mammary cancer is evidence of their being aware of the bad effects of ovarian function on cancer. Similarly many obstetric consultants advise immediate termination of a pregnancy occurring simultaneously with cancer, or even for a patient who has been treated for cancer. Fortunately the simultaneous occurrence of pregnancy and cancer is relatively rare, most authors reporting single cases or a very small personal series. A collection of cases based on a review of the literature on the subject is not entirely satisfactory for comparative study because of the omission of much important information.

It has been my privilege, through the courtesy of the various departments of Memorial Hospital, and from my own practice, to collect dur-

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The lesson to be drawn from Table XI should be self-evident.

TABLE XI. PERCENTAGE COMPARISON OF RESULTS

	COLLECTIVELY			PRIMIPARAS			MULTIPARAS		
	POOR	FAIR	EXC.	POOR	FAIR	EXC.	POOR	FAIR	EXC.
With primary repair	4	21	64	2	14	76	5	25	7
Without primary repair	72	22	6	69	21	10	76	17	54

In conclusion, I would suggest that the procedure of primary cervical repair be taught but not practiced, unless one has obtained some experience in this type of surgery. This experience is not difficult to acquire. Strict asepsis is of prime importance and only hospital equipment can give this strict asepsis.

Primary repair of the cervix is one more procedure in the practice of obstetrics that raises that practice to an art.

My experience with this series convinces me that primary cervical repair offers a safe, time-saving method of correcting or decreasing cervical pathology resulting from childbirth.

REFERENCES

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- (3) Williams, J. W.: Obstetrics, ed. 6, New York, D. Appleton-Century Co., p. 295.
- (4) Beck, A. C.: Obstetrical Practice, Baltimore, Williams & Wilkins Co., p. 151.

808 EUCLID AVENUE

Studdiford, William E.: Severe and Fatal Reactions Following the Intravenous Use of Gum Acacia Glucose Infusions, Surg., Gynec. & Obst. 64: 772, 1937.

The intravenous use of acacia solution may be dangerous and may result in serious reactions or in death. While serious reaction is far more likely to follow the use of improperly prepared (commonly called "impure") solution, the introduction of properly prepared acacia has been noted to be followed by deleterious changes in the quality and behavior of the blood. These changes, taking place to a more marked degree with the improperly prepared solution, may explain the nature of severe immediate reactions.

Hemorrhage and shock can be treated more safely by the use of the simpler saline or glucose infusions in combination with transfusion. The only justification for the intravenous use of acacia solution in the treatment of shock and hemorrhage is as a last resort when transfusion is unavailable. The method of preparation and condition of storage should be controlled with care.

The findings in the three autopsies reported are of significance. A special contraindication to its use exists in patients with damaged livers.

There is evidence that the acacia solution may interfere with the gaseous interchanges of the red cells, thus producing severe or fatal anoxemia.

There is evidence that acacia solutions may cause conglutination of the red cells, with resultant capillary blockage followed by edema and hemorrhage.

WM. C. HENSKE.

CASE 10.—H. K., 1921, thirty-one years of age, gravida iv. Adenocarcinoma of right breast; radical operation and postoperative x-ray. Full-term pregnancy in 1931. Abortion 1934 and 1935. First baby normal, now healthy boy of five and one-half years. Patient well fifteen years from operation and five years from first pregnancy.

CASE 11.—M. C., 1930, thirty-two years of age, gravida iii. Advanced adenocarcinoma of left breast, one and one-half months pregnant; operation and x-ray therapy of breast followed by abortion. Patient lived two months after abortion.

CASE 12.—A. R., 1934, thirty-five years of age, gravida ii. Adenocarcinoma of left breast seen first when eight months pregnant; treated with radium element pack at once; delivered of normal baby at term now twenty-six months. Patient is well twenty-eight months from time of treatment.

CASE 13.—A. N., 1926, seventeen years old, primigravida. Adenocarcinoma of right breast; treated with operation and radium and x-ray. Pregnant four and one-half years after operation; delivered at term. Normal child four years old today. Patient well nine years, six months from operation.

CASE 14.—D. S., 1933, thirty-five years old, gravida iii. Solid carcinoma of breast, bilateral; spontaneous abortion at 2 months; macerated fetus. No treatment of breast. Still alive 18 months from beginning of pregnancy.

CASE 15.—H. D., 1931, thirty-three years old, primigravida. Duet carcinoma of right breast; operated upon. Pregnant six months after operation; delivered at term of twins, both normal, but one died after three and one-half days. Mother at present well, five years and three months from operation.

CASE 16.—S. L., 1926, twenty-five years old, primigravida. Adenocarcinoma of right breast; induced abortion at three months, followed one month later by radical operation, x-ray, and radium. Died eighteen months from beginning of pregnancy.

CASE 17.—B. G., 1926, forty years of age, gravida ii. Carcinoma simplex of right breast; radical operation. Became pregnant thirty-two months later; induced abortion at two and one-half months. Alive and well six years from beginning of pregnancy when last seen in 1934.

CASE 18.—B. H., 1936, thirty-five years of age, two and one-half months pregnant when first seen. Spindle cell carcinoma of left breast; left radical mastectomy followed by postoperative x-ray; induced abortion at three and one-half months. Patient alive and well six months after operation.

CASE 19.—S. Z., 1928, thirty-four years of age, gravida ??, adenocarcinoma of breast. Hysterectomy and removal of metastatic carcinoma in the ovaries when two months pregnant. Breast treated with radium and x-ray; and simple mastectomy one year after abortion. Died two years and ten months from the beginning of pregnancy.

CASE 20.—J. W., 1927, thirty-eight years of age, gravida v. Adenocarcinoma of left breast; radical mastectomy, three months later became pregnant. Aborted by hysterotomy and tubal sterilization at three and one-half months. Died four years from beginning of pregnancy.

CASE 21.—C. G., 1935, twenty-nine years of age, primigravida. Operable carcinoma of right breast; radical mastectomy; induced abortion at two and one-half months. Alive one year from the mastectomy.

ing the past ten years a group of 54 patients suffering with malignant tumors who also had one or more pregnancies occurring either simultaneously with the appearance of the tumor or following its treatment. Although realizing that this is a small number from which to attempt to draw statistical conclusions, a study of these cases seems justified because of the rarity of the combination of conditions.

CASE REPORTS*

CASE 1.—L. Z., 1932, thirty-six years of age, gravida iii. Early cancer of the cervix when six and one-half months pregnant; radium applied locally; cesarean section and supracervical hysterectomy at eight months; postoperative radium in cervical stump plus external irradiation with x-ray. Baby born alive but died three days later of atelectasis; complete autopsy. Patient lived one year and one month from the beginning of pregnancy.

CASE 2.—L. L., 1935, thirty-seven years of age, gravida v. Advanced carcinoma of cervix discovered when 8 months pregnant; delivered vaginally at term. Treatment by irradiation postpartum. Normal baby and mother alive twenty-three months at present from the beginning of the pregnancy.

CASE 3.—F. T., 1935, thirty-one years old, gravida iv. Advanced carcinoma of cervix found when 4 months pregnant. Induced abortion; x-ray and radium one and one-half months after abortion. Alive, but not well, eight months later to present time.

CASE 4.—E. N., 1934, twenty-four years of age, gravida i. Advanced cancer of cervix found at term. Cesarean section and hysterectomy at term, with postoperative x-ray and radium; died eleven months after treatment, twenty-two months from beginning of pregnancy. Normal baby two and one-half years old.

CASE 5.—F. B., 1934, thirty-four years old, gravida iv. Moderately advanced carcinoma of cervix when one month pregnant. Induced abortion followed at once by x-ray and radium. Lived two years and one month from beginning of pregnancy.

CASE 6.—B. B., 1933, nineteen years of age, gravida ii. Embryonal carcinoma of ovary discovered growing rapidly at eight months. Cesarean section and oophorectomy; postoperative irradiation by x-ray; well two and one-half years with normal baby at present time.

CASE 7.—M. R., 1928, thirty-two years old, gravida i. Embryonal epidermoid carcinoma of urethra found at term. Normal baby now eight years old. Mother treated with radon seeds and external irradiation. Recurrence one year ago; treated with cautery excision. No evidence discovered at present.

CASE 8.—G. D., 1931, nineteen years old, gravida i. Embryonal carcinoma of ovary found at term; delivery by cesarean section followed by hysterectomy and postoperative radium and x-ray. Patient and normal baby well at present five and one-half years from beginning of pregnancy.

CASE 9.—M. O., 1929, forty years old, gravida i. Carcinoma of left breast noted when seven months pregnant. Antepartum x-ray of breast, delivered at term. Normal baby now six years of age. Postpartum x-ray and radium. Died fourteen months after treatment.

*"Present time" in the following case reports is as of June 1, 1936, when the statistics were compiled.

CASE 32.—J. C., 1930, thirty-two years old, gravida iii. Neurogenic sarcoma of supraclavicular region discovered when eight and one-half months pregnant; induced labor at eight and one-half months with healthy infant now five years, four months old. Three months after delivery the tumor was excised followed by x-ray therapy. Patient well six years from beginning of pregnancy.

CASE 33.—A. R., 1927, twenty-nine years of age, gravida iv. Neurofibrosarcoma of right groin, treated by excision and postoperative irradiation. Became pregnant in three years ten months following treatment. Delivery at term of normal healthy infant now six years of age. Patient well at present.

CASE 34.—C. I., 1923, twenty-two years of age, gravida iii. Sarcoma of lower jaw discovered when six months pregnant. Treated by jaw resection, delivered at term, baby healthy at birth. Patient died twelve years from beginning of pregnancy.

CASE 35.—M. Q., 1928, thirty-four years of age. Angiosarcoma of symphysis pubis discovered when four months pregnant; treated by excision; delivery at term of healthy baby. Postpartum x-ray treatment of the tumor. Four years later again pregnant; normal child at term resulting. Patient and both children all well eight years from beginning of first pregnancy.

CASE 36.—C. T., 1934, thirty-four years of age, gravida iv. Osteogenic sarcoma of left shoulder discovered when three months pregnant. Said to have had spontaneous abortion at three and one-half months, and immediately after this had shoulder disarticulation followed by Coley toxins. One year later again pregnant; delivered at term of healthy baby. Mother well two and one-half years from beginning of first pregnancy.

CASE 37.—A. M., 1927, eighteen years of age, gravida ii. Osteogenic sarcoma of scapula treated with x-ray. Eight months later became pregnant. Delivered at term of a healthy infant. Died twelve months from beginning of pregnancy.

CASE 38.—T. S., 1929, nineteen years old, gravida. Osteogenic sarcoma of right tibia treated with irradiation and Coley toxins. Pregnant seven months after treatment. Spontaneous delivery at term of healthy infant; postpartum x-ray therapy for tibia. Patient well five years and three months from beginning of pregnancy.

CASE 39.—P. M., 1924, fifteen years old, primigravida. Fibrosarcoma of back, treated with excision and postoperative x-ray. Pregnant ten years later; delivered at term of healthy infant. Well one year, ten months from beginning of pregnancy; twelve years from treatment of tumor.

CASE 40.—P. P., 1934, thirty-three years old, primigravida. Melanoma of back, noted when three months pregnant. Tumor treated by excision. Delivered by cesarean section at eight months; healthy infant. Postpartum x-ray to back. Patient died twenty-two months from beginning of pregnancy.

CASE 41.—S. B., 1933, twenty-eight years old, gravida ii. Melanoma of back noted when five months pregnant. Treated by excision. Induced labor at seven months, healthy infant alive and well today. Patient died twenty-one months from beginning of pregnancy.

CASE 42.—A. F., 1932, forty years old, gravida iii. Melanoma of scalp. Noticed activity of growth when six weeks pregnant. Induced abortion six weeks followed by excision and postoperative x-ray therapy for tumor. Died eighteen months from beginning of pregnancy.

CASE 22.—G. P., 1934, thirty-nine years, gravida v. Tubular carcinoma of right breast; treated with postoperative x-ray and radical mastectomy and postoperative radium with the element pack. Eight months and thirteen months after the operation the patient became pregnant and had induced abortions at three and six weeks, respectively. Alive two years after the mastectomy.

CASE 23.—F. S., 1934, thirty-five years of age, gravida iii. Infiltrating carcinoma of left breast discovered when the patient was delivered of a normal infant at term. Breast treated with local excision and x-ray five months after delivery. Patient is alive three years and eleven months from the beginning of pregnancy.

CASE 24.—M. N., 1932, gravida iv. Infiltrating duct carcinoma of right breast discovered when nine months pregnant. Delivered at term of a normal living infant. Breast treated with x-ray four months after delivery, followed by radical mastectomy. Patient is alive four years and ten months after.

CASE 25.—J. O., 1926, thirty-six years old, gravida iii. Operable carcinoma of left breast discovered when eight months pregnant. Radical mastectomy was performed. Patient delivered at nine months of living normal baby. Postoperative x-ray treatment of breast. Two years later again pregnant, aborted at two months. Alive two years and eight months from beginning of first pregnancy, six months from beginning of last pregnancy.

CASE 26.—I. R., 1934, thirty years old, primigravida. Solid carcinoma of left breast discovered when seven months pregnant. Delivered at term of normal living infant. Breast treated three weeks after delivery by local excision and x-ray followed by radical mastectomy and postoperative x-ray. Alive two years and eleven months from beginning of pregnancy.

CASE 27.—L. G., 1935, thirty-one years of age, primigravida. Solid adenocarcinoma of left breast discovered at term; delivery of normal living infant. Four months later was treated with x-ray only. Died seventeen months from beginning of pregnancy.

CASE 28.—D. E., 1922, twenty-five years of age, primigravida. Carcinoma of right breast; treated by radical mastectomy followed by postoperative x-ray. Seven months later became pregnant, delivered at term of normal living infant. Died two years and ten months after the mastectomy.

CASE 29.—N. S., 1934, twenty-one years of age, primigravida. Papillary adenocarcinoma of right breast discovered when patient was two months pregnant. Breast treated by excision followed by irradiation with radium element pack. Delivered at term of normal living baby. Two months later again pregnant, delivered of healthy baby at term. Patient well two years from beginning of first pregnancy.

CASE 30.—D. C., 1933, thirty-seven years old, gravida ii. Carcinoma of the right breast discovered when four months pregnant. Delivery at term of healthy infant. Breast treated by x-ray only three months after delivery. Patient well when last seen in August, 1935, three years and three months from beginning of pregnancy.

CASE 31.—C. G., 1932, thirty-five years old, primigravida. Myosarcoma of left ankle; treated by amputation and x-ray. Pregnant two years later. Delivered at term of normal living infant. Patient well at present, two years, ten months from beginning of pregnancy and four years, ten months from time of amputation.

CASE 54.—M. M., 1931, thirty years of age, gravida ii. Epidermoid carcinoma of tongue discovered when three months pregnant. The tongue was treated by radium followed by hemiglossectomy. Attempted x-ray abortion at three and one-half months completed mechanically five weeks later, resulting in a macerated but otherwise normal fetus. Following abortion the tongue received further irradiation. The patient died one year from the beginning of pregnancy.

The classification of patients as to age and type of tumor (Table I) shows that more than half of the patients studied were in the fourth decade, and only 7.5 per cent in the fifth decade. This perhaps explains

TABLE I. CLASSIFICATION OF PATIENTS STUDIED AS TO AGE AND TUMOR

DISEASE	NO.	2ND DECADE		3RD DECADE		4TH DECADE		5TH DECADE	
		No.	%	No.	%	No.	%	No.	%
Carcinoma cervix	5			1		4			
Carcinoma genito- urinary*	3	2				1			
Carcinoma breast	22	2		3		15		2	
Sarcoma	9	3		1		5			
Melanoma	6			2		3		1	
Lymphatic tumors and Hodgkin's disease	4			2		2			
Carcinoma stomach	2			1				1	
Carcinoma parotid	2	1		1					
Carcinoma tongue	1			1					
Total	54	8	14.8	12	22.2	30	55.5	4	7.5

*Ovary 2, urethra 1.

in part the rarity of pregnancy occurring in patients having malignant tumors. The actual incidence has not been expressed, but certain facts pertaining to the age incidence as a factor in the rarity of the combination of conditions are of interest. In reviewing the records of 141,946 pregnancy patients at New York Lying-In Hospital, I³² found only 5 patients recorded as having carcinoma of the cervix at the time of the pregnancy. Similarly, in reviewing¹³ 2,852 records of patients with carcinoma of the cervix at the Memorial Hospital, only the 5 patients with pregnancies included in this study were found. In a study³² of 200 patients with carcinoma of the cervix, the average age incidence was forty-six years.

Neill² quotes the following reports on incidence of pregnancy and carcinoma of the cervix:

Stöckel	18,000 pregnancies, 8 cases, 0.04 %
Hirst	12,538 pregnancies, 1 case, 0.008
Gross	1,538 pregnancies, 1 case, 0.065
Mendel	29,962 pregnancies, 24 cases, 0.08
University of Chicago	18,243 pregnancies, 2 cases, 0.01
Johns Hopkins	1,500 pregnancies, 2 cases, 0.3

Pack¹⁴ in his study of age and sex incidence of patients at Memorial Hospital presents some facts that further explain the rarity of the combined conditions. He found that in carcinoma of the cervix the maximal number of cases in any age

CASE 43.—D. E., 1924, twenty-three years old, primigravida. Melanoma of forearm, noticed when seven and one-half months pregnant. Induced labor, with living viable healthy child. Followed in one week by excision of tumor and postoperative x-ray. Patient died ten months from beginning of pregnancy.

CASE 44.—E. E., 1926, thirty-four years old, gravida iii. Melanoma of left foot treated by excision and postoperative x-ray of foot and groin. Four years and eight months later patient became pregnant. Delivery at term of healthy infant. Mother and baby well six years after birth of baby.

CASE 45.—B. W., 1934, thirty-six years old, gravida ii. Melanoma of right calf; treated by excision of tumor with postoperative x-ray of calf and groin. Became pregnant 6 months later. Tumor again excised during the pregnancy, with x-ray of calf and groin. Baby delivered prematurely at seven months but was normal and healthy at two years. Patient died one month after delivery.

CASE 46.—V. E., 1933, thirty-eight years old, gravida vii. Lympho-epithelioma of nasopharynx treated with x-ray. Became pregnant two years later. Aborted, sterilized by hysterectomy at two months. Had x-ray therapy following the abortion. Well fifteen months from beginning of pregnancy.

CASE 47.—E. A., 1932, twenty-nine years of age, gravida iii. Hodgkins' disease discovered when five months pregnant. Treated only with transfusions and delivered at term of a normal infant. X-ray therapy immediately following delivery. Died two years from beginning of pregnancy.

CASE 48.—H. B., 1930, thirty years of age. Lymphosarcoma of peritoneal lymph glands, discovered when two months pregnant. Spontaneous abortion followed exploratory celiotomy at two months. One month later the patient was treated with x-ray. Died four months from the onset of pregnancy.

CASE 49.—W. E., 1935, twenty-six years of age, gravida ii. Hodgkins' disease treated by x-ray. Two months later became pregnant. Hysterotomy and sterilization at two and one-half months; postoperative x-ray. Alive but not well one year from the beginning of pregnancy.

CASE 50.—M. C., 1930, forty-one years, gravida xxvi. Adenocarcinoma of the stomach discovered at term. Delivery resulted in a healthy infant. Five months postpartum gastrostomy and x-ray therapy for the tumor. Died sixteen months from beginning of pregnancy.

CASE 51.—H. W., 1928, twenty-seven years of age, gravida ii. Carcinoma of the stomach discovered when two months pregnant. Normal child in delivery at term. Postpartum radium and x-ray. Patient died sixteen months from beginning of pregnancy.

CASE 52.—N. W., 1934, twenty-two years of age, gravida ii. Epidermoid carcinoma of the parotid gland discovered when seven months pregnant. Untreated, the patient was delivered at term of a healthy infant. Two months postpartum the tumor was treated with radium and x-ray. Patient alive two years and three months from beginning of pregnancy.

CASE 53.—L. A., 1927, thirty years, primigravida. Adenocarcinoma of right parotid gland, treated by excision. One and one-half years later patient became pregnant. Delivered at term of healthy infant. During the pregnancy the tumor was treated with irradiation. Again pregnant three months after first birth, aborted at three and one-half months. Died two years and eleven months from beginning of first pregnancy.

rate of 22.5 per cent in a large series of patients with cancer of the cervix. No patient with cancer of the cervix became pregnant after treatment of the cancer;

In the breast group, Lee¹⁷ has noted that his curve of life in inoperable cancer of the breast is almost identical with the untreated group curve of Daland¹⁵ who reports the mean average of life in his breast cancer patients as thirty months;

In the nongenital group, Stone,¹⁸ reporting on Hodgkin's disease, found sixteen months as the average life for his entire group, and thirty-five months for the patients that responded to treatment. Craver¹⁹ quotes Sehreiner and Mattiek²⁰ as claiming two years and seven months as their average survival period in treated patients in Hodgkin's disease. The rapid fatal course of activated melanoma, sarcoma, and Hodgkin's disease is familiar to all surgeons.

In Table III each separate group and the totals show the prognosis is distinctly better for the patients having a pregnancy after the treatment of the malignant tumor than for patients who were pregnant at the time they were first seen with the tumor.

TABLE III. CLASSIFICATION AS TO LENGTH OF LIFE FROM TIME OF TREATMENT OF TUMOR, LOCATION OF TUMOR, AND WHETHER THE PREGNANCY OCCURRED WITH THE TUMOR OR FOLLOWED TREATMENT OF TUMOR

CLASSIFICATION	NO.	PREGNANT WHEN FIRST SEEN WITH TUMOR			PREGNANT AFTER TREATMENT OF TUMOR		
		NUMBER	LIVED 2 YEARS AFTER TREATMENT OF CARCINOMA		NUMBER	LIVED 2 YEARS AFTER TREATMENT OF CARCINOMA	
			NO. xx-1	%		NO.	%
Genitals	8	8x-2*	4xxx-1	50.0	0	0	0
Breasts	22	13x-1	6	46.1	9x-1	8xx-3	88.8
Nongenital	24	14x-1	4	28.5	10x-1	6	60.0
Total	54	35x-4	14	40.0	19x-2	14	73.6
Corrected total	48	31	14	45.1	17	14	82.3

*x, Still alive but not yet two years: excluded from figure. xx, Lived more than two years but died: not excluded from figure. xxx, Recurrence, carcinoma of urethra after six years, well one year: included in figure.

Believing that the length of life from the beginning of pregnancy might give more information as to the pregnancy's possible activating effect on the tumor, Table IV shows the comparative study of the sev-

TABLE IV. CLASSIFICATION AS TO LENGTH OF LIFE FROM BEGINNING OF PREGNANCY

CLASSIFICATION	NO.	PREGNANT WHEN FIRST SEEN WITH TUMOR			PREGNANT AFTER TREATMENT OF TUMOR		
		NUMBER	LIVED MORE THAN 2 YEARS		NUMBER	LIVED MORE THAN 2 YEARS	
			NO. xx-1	%		NO.	%
Genitals	8	8x-2*	4xxx-1	50.0	0	0	0
Breasts	22	13x-2	8xx-1	61.5	9x-2	7xx-1	77.7
Nongenital	24	14	6xx-2	42.8	10x-3	5	50.0
Total	54	35	18	51.4	19	12	63.1
Corrected total	45	31	18	58.0	14	12	85.7

*x, Still alive. xx, Lived more than two years from beginning of pregnancy but died. xxx, Recurrence, Carcinoma of Urethra after six years, well one year.

group was between forty-five and forty-nine years of age. In breast carcinoma one-third of all cases are forty-five to fifty-five years of age, the peak of the incidence is sixty to sixty-four years. In sarcoma the average age was 38.2 (which may explain the relatively large number of pregnant patients in this group). In carcinoma of the stomach the average age is fifty-four years, and it is twice as frequent in males as in females. In melanoma the average age is forty-eight years, male to female 2 to 1. One-half of the patients are beyond child bearing age.

Craver¹⁹ reported the average age of five-year survivors of Hodgkins' disease as thirty-four years and the rapidly fatal group as forty-four years.

Binkley³³ in approximately 600 female patients with cancer of the rectum had seen only 1 patient who also was pregnant. This patient went to term and was alive two years from time of treatment but is not included in this study.

Because of the paucity of available cases, it has been considered advisable to group the patients for comparative study according to the anatomic location of the diseased organ: Genital, breast, and non-genital.

In Table II in the genital group none of the 5 patients with pregnancy and carcinoma of the cervix when first seen lived five years, although two were still alive at the time of this writing. Only one of this genital group (carcinoma of urethra) had lived more than five years. None of the coincidental pregnancy and breast patients had lived five years although 8 are still alive. Of the breast patients in which pregnancy followed the treatment of the carcinoma, 44.4 per cent lived more than five years. There were no patients in the genital group in which pregnancy followed the treatment of the tumor, but it is perfectly evident from the breast group, the nongenital, the total, and the corrected total (in which patients still alive but not having lived five years from treatment are discarded) that the prognosis is better for the patient if the pregnancy occurs after the tumor has been treated than if it occurs simultaneously with the appearance of the tumor.

TABLE II. CLASSIFICATION AS TO LENGTH OF LIFE FROM TIME OF TREATMENT OF TUMOR AND AS TO WHETHER THE PREGNANCY WAS COINCIDENTAL WITH OR FOLLOWED TREATMENT OF TUMOR

CLASSIFICATION	NO.	PREGNANCY WITH UNTREATED TUMOR			PREGNANCY FOLLOWING TREATMENT OF TUMOR		
		NUMBER LIVED 5 YEARS			NUMBER LIVED 5 YEARS		
Genitals	8	8x-4*	NO. 1	% 12.4	0	NO. 0	% 0
Breasts	22	13x-8	0	0	9x-2	4	44.4
Nongenital	24	14x-2	3xx-1	21.4	10x-3	4	40.0
Total	54	35x-14	4	11.4	19x-5	8	42.1
Corrected total	35	21	4	19.0	14	8	57.1

*x, Still Alive. xx, Lived more than five years but died.

As so few patients in the classification "Pregnant When First Seen" lived five years, a similar comparison has been made in Table III, using two years of life from the treatment of the malignant tumor as the borderline of classification. This short period of life seems justified in studying the effects of pregnancy on malignant tumors, because:

In the genital group, only 1 of 5 pregnant cervix patients lived two years (died two years and one month), yet Healy¹⁶ has reported an absolute five-year salvage

TABLE VI. PARITY, TREATMENT OF PREGNANCY, LIFE FROM BEGINNING OF PREGNANCY

CLASSIFICATION	TOTAL	ABORT- ED	WELL MORE THAN TWO YEARS	NOT ABORT- ED	WELL MORE THAN TWO YEARS		
<i>Primigravid</i>							
Genitals	3	0	NO. 0	% 0	3	NO. 2	% 66.6
Breasts	8	1x-1*	0	0	7	6xx-2	85.7
Nongenitals	7	3	0	0	4x-1	3x-1	75.0
Totals	18	4x-1	0	0	14x-1	11	78.5
Corrected totals	16	3	0	0	13	11	84.5
Well two years Per cent	11 68.7						
<i>Multigravid</i>							
Genitals	5	4x-1	2	50.0	1x-1	0	0.0
Breasts	14	9x-3	4	44.4	5	5	100.0
Nongenitals	17	7x-2	2	28.5	10	6xx-1	60.0
Total	36	20x-6	8	40.0	16x-1	11	68.7
Corrected total	29	14	8	57.1	15	11	73.3
Well two years Per cent	19 65.5						

*x, Still alive but less than two years from beginning of pregnancy. xx, Lived two years from beginning of pregnancy but died.

Only the 35 patients who were pregnant when first seen for malignant tumor are included in Table VII, which is a consideration of the effect on the tumor of the stage of the pregnancy (taking 4 months as an

TABLE VII. PATIENTS PREGNANT COINCIDENTAL WITH UNTREATED TUMOR, ADVANCEMENT OF PREGNANCY WHEN FIRST SEEN, TREATMENT OF PREGNANCY, LENGTH OF LIFE FROM BEGINNING OF PREGNANCY

CLASSIFICATION	TOTAL	ABORT-ED	WELL MORE THAN TWO YEARS	NOT ABORT-ED	WELL MORE THAN TWO YEARS		
<i>Less Than Four Months Pregnant</i>							
Genitals	2	2x-1*	NO. 1xx-1	% 50.0	0	0	0
Breasts	6	4x-2	0	0.0	2	2	100.0
Nongenitals	7	5	2	40.0	2	1	50.0
Total	15	11	3	27.2	4	3	75.0
<i>More Than Four Months Pregnant</i>							
Genitals	6	2	1	50.0	4x-1	2xxx-1	50.0
Breasts	7	1	1	100.0	6	4	66.6
Nongenitals	7	3	1	33.3	4	3xx-2	75.0
Total	20	6	3	50.0	14	9	64.2

*x, Still alive. xx, Lived more than two years from beginning of pregnancy, but died. xxx, Recurrence, carcinoma of urethra after six years, well one year.

empirical borderline), and whether, or not, the pregnancy was interrupted, as measured by the length of life from the beginning of pregnancy.

eral groups and totals as to whether the patient was pregnant when first seen with tumor, or became pregnant after treatment of tumor. The results are similar to those of Tables II and III.

Table V is a study of the effects of the treatment of the pregnancy on the tumor as measured by the length of life from the beginning of the pregnancy.

TABLE V. TREATMENT OF PREGNANCY, AND LIFE FROM BEGINNING OF PREGNANCY

CLASSIFICATION	TOTAL	PREG- NANCY INTER- RUPTED	WELL MORE THAN TWO YEARS	PREG. NOT INTER- RUPTED	WELL MORE THAN TWO YEARS		
<i>Pregnant When First Seen</i>							
Genitals	8	4x-1*	NO. 2xx-1	50.0	4x-1	NO. 2xxx-1	50.0
Breasts	13	4x-2	0	0.0	9	8	88.8
Nongenitals	14	8	2	25.0	6	3	50.0
Total	35	16	4	25.0	19	13	68.4
Corrected total	31	13	4	30.7	18	13	72.2
<i>Pregnant After Treatment for Carcinoma</i>							
Genitals	0	0	0	0	0	0	0
Breasts	9	5x-2	3xx-1	60.0	4	4xx-1	100.0
Nongenitals	10	3x-2	0	0	7x-1	5xx-1	71.4
Total	19	8	3	37.5	11	9	81.8
Corrected total	14	4	3	75.0	10	9	90.0

*x, Still alive. xx, Lived more than two years from beginning of Pregnancy, but died. xxx, Carcinoma of Urethra recurrence after 6 years, well now 1 year.

In the genital group of 5 cervix cases, 3 were interrupted and 2 were not. Three patients died, 2 in less than two years and 1 (which was interrupted) lived two years and one month from the beginning of pregnancy. Two are still alive, but have not yet passed the two-year period. Of the remaining cases in the genital group (2 carcinoma of the ovary, 1 carcinoma of the urethra), all three lived more than two years. In one of these the pregnancy was interrupted.

From the breast and nongenital groups and from the totals, it is evident that patients had a better prognosis if the pregnancy was not interrupted. This is especially noticeable in the breast group that were pregnant when first seen with the tumor.

A comparative study of parity with the effect of abortion on the tumor as measured by the length of life from the beginning of pregnancy is shown in Table VI. The patients are not separated into groups as to whether, or not, the tumor and pregnancy occurred simultaneously. There is very little difference between primigravidas and multigravidas as to total percentages well two years, but it is a rather striking fact that, of the aborted primigravidas, none remained well two years. It could possibly be argued that the primigravidas were younger than the multigravidas, and, therefore, had a worse prognosis anyhow, but the primigravidas who were not aborted did practically as well as the corresponding multigravidas.

TABLE IX. INTERVAL BETWEEN END OF PREGNANCY AND BEGINNING OF TREATMENT FOR THE TUMOR, LENGTH OF LIFE FROM BEGINNING OF PREGNANCY

CLASSIFICATION	NO.	TREATMENT AT ONCE OR LESS THAN ONE MONTH			INTERVAL MORE THAN ONE MONTH		
		NO.	LIVED MORE THAN TWO YEARS		NO.	LIVED MORE THAN TWO YEARS	
			NO.	%		NO.	%
Genitals	8	4x-1*	2xx-1	50.0	4x-1	2	50.0
Breasts	13	8x-2	5xx-1	62.5	5	3	60.0
Nongenitals	14	9	4xx-1	44.4	5	2	40.0
Total	35	21	10	47.6	14	6	44.4
Corrected total	31	18	10	55.5	13	6	46.1

*x, Still alive. xx, Lived more than two years from beginning of pregnancy but died. xxx, Recurrence, carcinoma of urethra after six years, well one year.

Table X indicates that there is some slight advantage in treating breast carcinoma before the end of the pregnancy, but that there is a definite disadvantage in treating nongenital patients, taken as a group, before the end of the pregnancy.

TABLE X. COMPARISON OF PREGNANT PATIENTS RECEIVING TREATMENT DURING PREGNANCY WITH THOSE NOT RECEIVING TREATMENT AS TO LENGTH OF LIFE FROM BEGINNING OF PREGNANCY

CLASSIFICATION	ELIGIBLE	RECEIVING TREATMENT	ALIVE MORE THAN TWO YEARS		NOT RECEIVING TREATMENT	ALIVE MORE THAN TWO YEARS	
			NO.	%		NO.	%
Genitals	8	4x-1*	2xx-1	50.0	4x-1	2	50.0
Breasts	13	3x-1	2xx-1	66.6	10x-1	6	60.0
Nongenitals	14	6	1xx-1	16.6	8	4	50.0
Total	35	13	5	38.4	22	12	54.5
Corrected total	31	11	5	45.4	20	12	60.0

*x, Still alive but less than two years. xx, Lived two years but died.

This is somewhat in accordance with the theories of Stöckel,⁴ Weibel,³ and others, that pregnancy retards the growth of the tumor, but is probably due to the type of tumor considered. Miller,²¹ Claye,²² Oldfield,²³ and Neill² report patients with carcinoma of the cervix in the last trimester of pregnancy treated successfully by hysterectomy and postoperative irradiation. Berkeley,²⁴ Neill,² Van Rooy,²⁵ and Mendel²⁶ cite patients with carcinoma of the cervix treated with irradiation during the pregnancy. All agree that after the termination of the pregnancy cancer grows rapidly. The 5 cervix cases here are not sufficient to prove which is the proper choice of treatment. The one patient treated in the early trimester of pregnancy with irradiation lived the longest in the group (two years, one month) but died. Two patients having hysterectomy, 1 following irradiation during the last half of pregnancy and the other with irradiation following the hysterectomy, lived only thirteen months and twenty-two months, respectively. The author agrees with Neill that in the early months the pregnancy should be ignored and irradiation therapy completed, adding mechanical abortion only if the irradiation fails to abort. In the last half of pregnancy, however, the patient should be treated with local irradiation, delivered by cesarean section when the child is viable, but the author feels that the supracervical portion of the uterus should be removed to prevent drainage through the diseased cervix. This, however, is theory and is neither proved nor disproved by Table X.

There seems to be a distinct disadvantage, as shown by the totals, in early interruption of the pregnancy, especially in the breast group. There is a slight advantage in early over late abortion in the non-genital group. The patients whose pregnancies were not interrupted did as well or better than those who were aborted, regardless of the stage of the pregnancy when first seen with the tumor.

In Table VIII, which includes only the 19 patients that became pregnant after the treatment of the tumor, there would seem to be some

TABLE VIII. PATIENTS BECOMING PREGNANT AFTER TREATMENT OF THE TUMOR COMPARED AS TO INTERVAL OF TIME BETWEEN TREATMENT OF TUMOR AND PREGNANCY, LENGTH OF LIFE FROM BEGINNING OF PREGNANCY, AND TREATMENT OF PREGNANCY

CLASSIFICATION	TOTAL	ABORT- ED	WELL MORE THAN TWO YEARS	NOT ABORT- ED	WELL MORE THAN TWO YEARS
<i>Interval Less Than Two Years</i>					
Genitals	0	0	NO. 0	0	NO. 0
Breasts	6	4x-2*	2xx-2	2	2xx-1
Nongenitals	5	2x-1	0	3	2xx-1
Total	11	6	2	5	4
Corrected total	8	3	2	5	4
Per cent well	75.0				80.0
<i>Interval More Than Two Years</i>					
Genitals	0	0	0	0	0
Breasts	3	1	1	2	2
Nongenitals	5	2	1	3x-1	2
Total	8	3	2	5	4
Corrected total	7	3	2	4	4
Per cent well	85.7				100.0

*x, Still alive. xx, Lived more than two years from beginning of pregnancy but died.

slight advantage in the pregnancy not occurring within two years after treatment, as shown by the total percentages remaining well two years from the time of the beginning of pregnancy. No patient in the genital group became pregnant after treatment of the tumor. It appears to be a distinct advantage in all groups to allow the pregnancy to continue regardless of the interval since the treatment of the tumor. The two aborted cases in the nongenital group, where less than two years had elapsed since treatment, were 1 patient with Hodgkin's disease and 1 with melanoma. These 2 cases and the 4 aborted breast cases in this time group would suggest that the abortion stirred up activity of the disease.

Table IX shows some advantage in treatment of the tumor being started before the end of the pregnancy, or within one month after the pregnancy ended, over a delay of more than one month. This advantage as shown here is surprisingly slight. Only patients pregnant when first seen with malignant tumors are included in this table.

the malignant tumor. Two of the patients with lymphatic tumors pregnant after the treatment of the tumor are still alive, but it is less than two years since the beginning of the pregnancy.

Table Xc shows that certain types of nongenital malignant tumors (melanomas) have a poor prognosis if treated during pregnancy. Unfortunately for comparison, all patients having melanoma and eligible for treatment during the pregnancy were treated, and the pregnancies were all also terminated prematurely. (One abortion at six weeks, 3 induced labor at seven, seven and one-half, and eight months, respectively.) Certainly these patients met a rapidly fatal end and suggest activation of these tumors by treatment of the tumor or by the abortion, when they were apparently quiescent during the pregnancy.

TABLE Xc. COMPARISON OF PATIENTS WITH NONGENITAL TUMORS RECEIVING TUMOR TREATMENT DURING PREGNANCY WITH THOSE NOT RECEIVING TREATMENT, AS TO LENGTH OF LIFE (TWO YEARS FROM BEGINNING OF PREGNANCY)

CLASSIFICATION	ELIGIBLE	RECEIVING TREATMENT	ALIVE MORE THAN TWO YEARS	NOT RECEIVING TREATMENT	ALIVE MORE THAN TWO YEARS
Sarcoma	4	2	2*	2	2
Melanoma	4	4	0		
Lymphatic tumor	2			2	0

*One patient died after twelve years.

Table XI shows 31 cases irradiated during or preceding pregnancy, 11 during and 20 preceding, with no deformity of the fetus, although the condition of the fetus was not recorded in 2 of the breast cases which had been irradiated previous to the pregnancy.

TABLE XI. FETUS AT BIRTH AFTER IRRADIATION

CLASSIFICATION	TOTAL	IRRADIATION DURING PREGNANCY			IRRADIATION PRECEDING PREGNANCY		
		NO.	NORMAL	DEFORMED	NO.	NORMAL	DEFORMED
Genitals	1	1	1	0	0	0	0
Breasts	16	6	6	0	10	8*	0
Nongenitals	14	4	4	0	10	10	0
Total	31	11	11	0	20	18	0

*Two cases not recorded.

The one patient in the genital group who was irradiated during the pregnancy had a carcinoma of the cervix, irradiated locally with 2,500 mc. hr. of radium at six and one-half months and delivered by cesarean section at eight months. The baby was normal in appearance, born alive but died three days later. A complete autopsy, including serial sections of the brain, revealed only atelectasis as the cause of death. No malformed baby occurred in this group of 54 cases. This is quite contrary to the impression given in reports by Neill,² Mendel,²⁶ Abels,²⁷ Stettner,²⁸ and Bailey and Bagg,²⁹ and involves the stage of the pregnancy when pelvic irradiation was administered. The absence of deformity of the fetus in this series is probably be-

Because of the marked known difference in behavior of the various types of nongenital malignant tumors that were available for study, it has seemed advisable to consider separately the three main types: sarcoma, melanoma, and lymphatic tumors.

Table XA compares each of the three types as to the length of life from the beginning of the pregnancy, and whether the pregnancy occurred simultaneously with the tumor, or followed the treatment of the tumor.

In the sarcoma group one patient with osteogenic sarcoma of the scapula, treated when five months pregnant and delivered at term, died three months after delivery. All but three patients with sarcoma lived more than five years. One died twelve years after the original tumor.

One patient with Hodgkin's disease died three years and three months after the beginning of the pregnancy.

It is obvious that the prognosis is better in each type if the pregnancy follows the successfully treated tumor rather than if it occurs simultaneously with the tumor.

TABLE XA. CLASSIFICATION OF NONGENITAL TUMORS AS TO LENGTH OF LIFE AND TIME RELATIONSHIP TO OCCURRENCE OF PREGNANCY

CLASSIFICATION	NO.	PREGNANT WITH UNTREATED TUMOR		PREGNANT FOLLOWING TUMOR TREATMENT	
		NO.	LIVED MORE THAN TWO YEARS	NO.	LIVED MORE THAN TWO YEARS
Sarcoma	9	5*	4	4	4
Melanoma	6	4	0	2	1
Lymphatic tumor	4	2	0	2	1†

*One patient died; sarcoma of scapula; treated when five months pregnant; delivered at term; died three months postpartum.

†Hodgkin's disease; lived three years, three months; died.

From Table XB it is evident that each group had a better prognosis if not aborted regardless of the time relationship of the pregnancy to

TABLE XB. CLASSIFICATION OF NONGENITAL TUMORS AS TO LENGTH OF LIFE FROM BEGINNING OF PREGNANCY AND AS TO TREATMENT OF PREGNANCY

CLASSIFICATION	TOTAL	PREG- NANCY IN- TERRUPTED	WELL MORE THAN TWO YEARS	PREG- NANCY NOT INTER- RUPTED	WELL MORE THAN TWO YEARS
<i>Pregnant When First Seen With Malignant Tumor</i>					
Sarcoma	4	2	2*	2	2
Melanoma	4	4	0		
Lymphatic tumor	2	1	0	1	1†
<i>Pregnancy Occurring After Treatment of Tumor</i>					
Sarcoma	5			5	4
Melanoma	2			2	1
Lymphatic tumor	2	2‡	0		

*Well only two years at present.

†Died two years, one month.

‡Still alive.

Because of the paucity of available cases, the stage of the tumor has not been considered. This fact, and the variability of behavior of the various types of tumors studied, prohibits didactic conclusions. The following conclusions, however, are at least suggestive.

CONCLUSIONS

I. Concerning the Patient:

A. Pregnancy is detrimental to, and should be prevented in, patients having unarrested malignant tumors.

B. Growing malignant tumors may be temporarily retarded by pregnancy but the growth is accelerated after the termination of the pregnancy.

C. Pregnant patients with malignant tumors have a better prognosis:

1. If the pregnancy is not interrupted;

2. If the pregnancy follows treatment of the tumor rather than occurring simultaneously with it. This is true whether the length of life from the time of treatment of the tumor or the length of life from the beginning of pregnancy is taken for comparison. The latter gives a more accurate measure of the effect of the pregnancy upon the tumor;

3. If, in patients becoming pregnant after the tumor therapy, more rather than less than two years have elapsed since the tumor therapy;

4. If, in the breast and nongenital groups, the patient is not aborted, regardless of the time relationship of the pregnancy to the occurrence of the tumor. This is possibly also true in the genital group, but in the early months of pregnancy the patient is usually aborted by the tumor therapy anyhow. In this series no patient in the genital group became pregnant after the tumor therapy;

5. If the breast and genital tumors are treated before the end of the pregnancy. It is of distinct advantage to the patient to treat these tumors and ignore the pregnancy, but it is better for the patients with certain nongenital tumors not to be treated until the pregnancy is ended, especially with melanoma.

D. As to the stage of the pregnancy (using four months as an empirical borderline) when the patient was first seen: If the patient is aborted, there is some slight advantage in early over late abortion in the nongenital group, but a distinct disadvantage in the breast group and total. All groups fared better if not aborted, regardless of the stage of the pregnancy when first seen.

E. As to Parity: Abortion was especially disastrous to primigravid women, whereas both primigravid and multigravid women did about equally well if not aborted.

cause only one of the genital group was irradiated during pregnancy and that patient was irradiated in the latter half of the pregnancy. None of the genital group had pregnancies after irradiation.

Ten of these pregnancies resulted in nonviable abortions, either induced or spontaneous, but only 3 were known to be definitely spontaneous abortions. Careful autopsy dissection was not performed on these fetuses, but grossly they were reported to appear normal. One patient (carcinoma of tongue) had an attempted x-ray abortion at three and one-half months with induced mechanical abortion completed five weeks later. A macerated, but otherwise grossly normal, fetus resulted.

Table XII shows that in the breast and nongenital groups the time of treatment of the tumor in relation to the pregnancy has no effect on the normalcy of the offspring which reach viability, for all the offspring were at least grossly normal.

TABLE XII. NORMALCY OF OFFSPRING REACHING VIABILITY WITH CLASSIFICATION AS TO TIME RELATIONSHIP BETWEEN TREATMENT OF TUMOR AND PREGNANCY, AND THE ADVANCEMENT OF THE PREGNANCY AT TIME OF TREATMENT OF TUMOR

CLASSIFICATION NO. PATIENTS CONDITION OF	TOTAL	NO TREATMENT DURING PREG- NANCY		TREATED DURING PREGNANCY			TREATED BEFORE PREGNANCY	
		NO.	NORMAL	1-4 MO.	4 MO. TO TERM	NORMAL	NO.	NORMAL
Fetus								
Genitals	6	5	5		1	10-1*		
Breasts	14	6	6	1v-1	1	2	6x-1	6
Nongenital	21	8	8	4v-1	1	5	8	8
Total	41	19	19	5	3	8	14	14

*o, Normal but died.

v, Two pregnancies, 1 before, 1 during treatment, both children normal.

x, Twins, both normal grossly, but 1 died.

Of 41 viable offspring that were grossly normal at birth, 25 are known at present to be normal healthy children, one to ten years of age, 8 of them are more than five years of age, 1 child died three and one-half days after birth, 1 twin died three days after birth, 1 child was killed by an automobile, 13 children (known to be normal at birth) could not be traced.

SUMMARY

In an effort to determine the effect of pregnancy on malignant tumors, 54 patients with malignant tumors who were also pregnant have been studied. The patients have been grouped for comparative consideration according to the location of the tumor; i.e., genital, breast, and nongenital.

No attempt has been made to establish the absolute incidence of occurrence of the combination of the conditions, but the rarity of the combination is best explained by the fact that the majority of patients developing malignant tumors are beyond childbearing age, or in the last decade of childbearing.

CHEMICAL DETERMINATION OF PREGNANCY BY THE VISSCHER-BOWMAN TECHNIQUE

CHARLES DRABKIN, A.B., M.D., AND SIEGFRIED GOLDSCHMIDT, M.D.,
St. Louis, Mo.

(From the Department of Obstetrics and Gynecology, Washington University School of Medicine, the St. Louis Maternity Hospital and Barnes Hospital)

IN 1934, Visscher and Bowman reported a chemical test made on urine for the diagnosis of pregnancy. In a series of 317 cases, their test was 93.05 per cent accurate. That same year, J. G. Menken applied this test to 23 cases, with a correct result in 95.65 per cent. C. Dolff in 1935, studied 83 patients and found the test accurate in 92.77 per cent. Up to that time it seemed that it compared in efficiency quite favorably with the still more accurate Aschheim-Zondek test.

We undertook an investigation of the reliability of this test by examining every day the urine of normal, nonpregnant women over a period of two consecutive menstrual cycles. We began our work in February, 1936, and followed the Visscher-Bowman technique, Method A.

Their procedure is as follows: "To 1 c.c. of urine is added one drop of 0.5 per cent hydrogen peroxide. This is shaken and allowed to stand for three minutes, after which are added 5 drops of a 1 per cent aqueous solution of phenylhydrazine hydrochloride, 5 drops of a 5 per cent aqueous solution of methyl cyanide, followed by 5 drops of concentrated hydrochloric acid. It is then put into a boiling water-bath and allowed to react for twenty-five minutes. After this time the reaction is said to be positive if russet color develops and a flocculent precipitate appears. A negative reaction is shown by the absence of a precipitate or the presence of a powdery one and usually a straw color. All reagents should be fresh at the time tests are made."^{*} All of the laboratory work was carried out by one of us (C. D.). Because of the inability to obtain daily specimens from all of our subjects, we can report only on 25 complete cases.

Our subjects were not married at the time this test was made. Three of the women had been married, and one had a four year old child. The age incidence was as follows: Between the ages of eighteen and twenty-five there were 22 women, the remaining 3 were between thirty-seven and forty-one years.

The shortest cycle was twenty-four days, in a woman who stated that she menstruated "regularly" every twenty-eight to thirty days. Her following cycle was of a twenty-nine-day type. Similar discrepancies were observed in others.

^{*}The chemicals used were: Merck's superoxol. Eastman Kodak Company's phenylhydrazine hydrochloride and acetonitrile.

II. Concerning the Fetus:

A. Irradiation of breast and nongenital tumors in pregnant women has no tendency to produce malformed babies.

B. In the genital group irradiation of the pelvic regions will usually produce abortion in the early months of pregnancy. This series sheds no light on the effect on the fetus of irradiation of the pelvis in the first half of pregnancy because no patient receiving such treatment went to viability.

C. In the latter months of pregnancy carcinoma of the cervix can be irradiated locally without affecting the baby or producing abortion.

D. Of 41 known viable normal offspring at birth, only 25 could be traced at the present time. These show no evidence of any bad effects of tumor therapy at the present time (one to ten years of age).

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In the repair of obstetric lacerations of the perineum, regardless of their extent, Mahon advises against the use of catgut. He is enthusiastic about the exclusive use of horsehair, not only for closure of the perineal body, but also for the anal sphincter and rectal wall. In nearly all cases, the horsehair sutures are spontaneously expelled between the sixth and fifteenth days. They are literally "defecated" by the patient.

TABLE II

NO. OF PA-TIENTS	GESTATION IN WEEKS	POSITIVE	NEGATIVE
8	8 weeks	6 (75.0 per cent)	2 (25.0 per cent)
4	10 weeks	3 (75.0 per cent)	1 (25.0 per cent)
5	12 weeks	4 (80.0 per cent)	1 (20.0 per cent)
10	12-16 weeks	7 (70.0 per cent)	3 (30.0 per cent)
10	16-20 weeks	4 (40.0 per cent)	6 (60.0 per cent)
11	20-24 weeks	7 (63.7 per cent)	4 (36.6 per cent)
15	24-28 weeks	11 (73.3 per cent)	4 (26.6 per cent)
13	28-32 weeks	11 (84.6 per cent)	2 (15.4 per cent)
13	32-36 weeks	9 (69.2 per cent)	4 (30.7 per cent)
15	36 to term	13 (86.6 per cent)	2 (13.3 per cent)
Total: 104		75 (72.1 per cent)	29 (27.7 per cent)

DISCUSSION

All of the control specimens were examined for specific gravity, reaction, albumin, and sugar. We noted in our nonpregnant women that concentrated urines gave almost invariably false positive Visseher-Bowman reactions, especially if the concentration was above 1.025. Every such specimen of urine was then diluted until its specific gravity was 1.018 to 1.020, at which dilution the reaction usually became negative. The urines with false positive reactions in the cases of acute salpingitis, as well as the correctly positive reacting urines of pregnancy, could be diluted to 1.012 and yet give a positive Visseher-Bowman reaction.

The addition of male whole blood to a negative urine did not alter the reaction of the test.

In our series of 25 nongravid women, only four of the subjects gave a negative Visseher-Bowman reaction throughout the cycle, with the exception that some time during the actual flow, we did get a positive reaction. In two of these women, the specific gravity of the urine was always less than 1.020.

After our experiments were completed, two additional reports appeared on this subject. Ernst Wiesener reported his observations made on 230 subjects, 141 of whom were in various stages of pregnancy, and 89 were not pregnant. In the latter series, 67 were healthy and 22 had some adnexal or uterine disease. In the pregnant group, his accurate results were 93.4 per cent. In the healthy, nonpregnant individuals, he reported 92.5 per cent accurate results and 86.3 per cent in the sick, nongravid women.

In November, 1936, Oscar Frankl and Paul Engel published their results in a series of 200 pregnant and nonpregnant women. Their table is here reproduced as Table III.

Experimentally, Dolfi and later Wiesener proved that the Visseher-Bowman reaction depends upon a certain concentration of prolan in the urine. In the presence of 2 R. U. of prolan in the urine of healthy, nonpregnant women, the reaction was negative. When the concentration was increased to 3 R. U., the reaction was questionable, but 4 R. U.

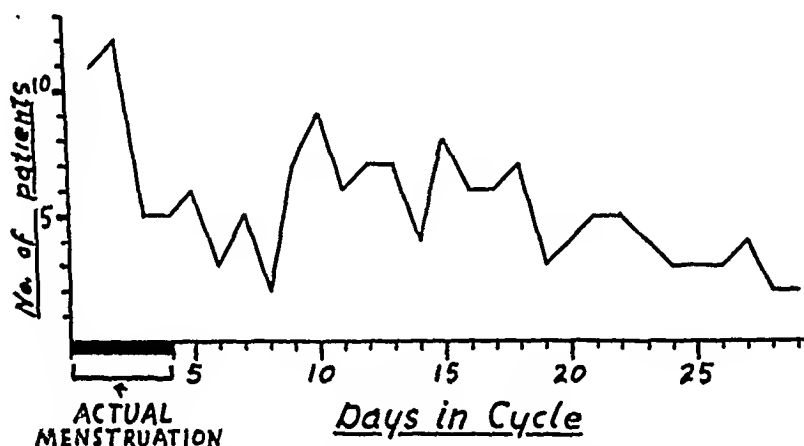
The menstrual flow in our patients varied from three to six days. Twenty-two flowed for four days, 17 flowed for five days, and 6 flowed for six days.

During the active menstrual flow, the positive Visseher-Bowman reactions were as shown in Table I.

TABLE I

DAY OF FLOW	NUMBER OF CASES	NUMBER POSITIVE	PERCENTAGE
First	25	11	44.0
Second	25	12	48.0
Third	25	5	20.0
Fourth	22	5	22.7
Fifth	17	4	23.5
Sixth	6	1	16.6

Graph 1 charts the positive Visscher-Bowman reactions during an entire cycle—considering the wrong positive reaction only for a four-



Graph 1.—Showing the number of positive Visscher-Bowman reactions out of 25 normal, nonpregnant women during their menstrual cycle.

day menstrual flow, because out of the 25 women, 22 had a four-day flow. In a general way the wrong positives declined gradually in the course of the cycle after the second day of the flow and the tenth day.

We also made tests with the urine obtained: (a) at the time of delivery (catheterized specimen), (b) at various periods during pregnancy, (c) in ectopic gestations, and (d) in cases of acute salpingitis with fever. Out of 36 specimens obtained at the time of delivery of a live, full-term fetus, 33 gave a positive reaction (91.7 per cent) and 3 were negative (8.3 per cent). Six out of 7 ectopic pregnancies later confirmed at operation, gave positive reactions (85.7 per cent). Out of 9 patients with acute salpingitis, 5 gave a positive reaction (55.5 per cent) and 4 gave a negative reaction (44.4 per cent).

In examining the urine at various stages during pregnancy, our findings were as shown in Table II.

6. The above test gave a positive reaction in 55.5 per cent and a negative reaction in 44.4 per cent of 9 patients with acute inflammatory salpingitis.

7. Thirty-six catheterized specimens at the time of delivery at full term, gave 91.7 per cent positive results and 8.3 per cent negative results.

8. The tendency of false positive reactions increases with the increase in the specific gravity of the urine above 1.018-1.020.

CONCLUSIONS

1. As a result of our investigation, we cannot consider the Visseher-Bowman chemical test for the determination of pregnancy as reliable.

2. Its inaccuracy is due to the fact that many highly concentrated urines give false positive reactions in nonpregnant women. The test is entirely too sensitive, since by this method we can determine the presence of 4 R. U. of prolactin in 1 c.c., and the urine from many nonpregnant women will equal or exceed such prolactin concentrations.

3. The test may prove of practical value in determining prolactin concentration above 3 R. U. in 1 c.c. of urine.

NOTE: Bohuslav Ostadol (in *Zentralbl. f. Gynäk.* 61: 266, 1937) just made a claim that the positive result of the Visseher-Bowman reaction is not due to the presence of prolactin A but probably to chemical substances, possibly disaccharides.

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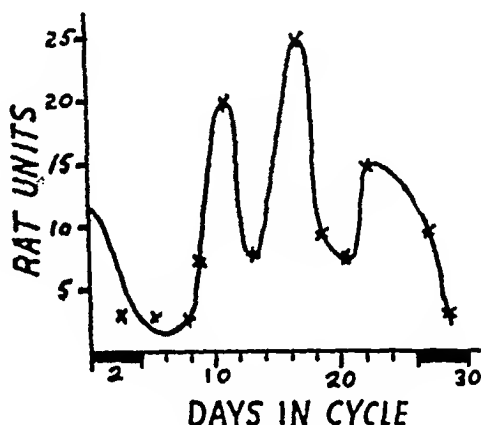
The author was interested in finding out whether twins share equal risks if the traumatism of labor is excluded. He studied the records of twins delivered at the Baudeloque clinic and found that among 131 twins born during the past seven years who weighed more than 2,000 gm., all of the first twins but only 128 of the second twins were born alive. At the tenth day, 129 of the first-born twins were still alive but only 119 of the second born. A student (Miss Reingevire) was delegated to investigate 184 twins delivered in the Nancy clinic. She found that, whereas, 154 of the first born were delivered alive, only 145 of the second twins were born alive. It was also found that the weight curves of the second twins during the stay in the hospital lagged behind those of the first born. The author found that the second twin usually weighed more than the first one, yet in spite of this, it ran a greater risk in being born. Second twins presented in an abnormal manner more frequently than first born. Hence operative intervention was necessary more frequently for their delivery.

J. P. GREENHILL.

TABLE III

	NUMBER RIGHT		WRONG
Nonpregnant	34	15 (44.1 per cent)	19 (55.9 per cent)
Early pregnancy (up to the second of the third month)	24	17 (70.8 per cent)	7 (29.2 per cent)
Pregnant (third month to term)	142	98 (69.0 per cent)	44 (31.0 per cent)
Total	200	128 (64.0 per cent)	72 (36.0 per cent)

of prolactin gave a strongly positive reaction. We repeated this experiment and essentially agree with their findings. The fact that we were able to get positive results in nonpregnant women especially in concentrated urines, then seems to mean that these urines had at least 4 R. U. of prolactin in the 1 c.c. of urine used for the test. Pedersen-Bjergaard has recently published an interesting article on the prolactin content in the urine during the menstrual cycle of nonpregnant women. His work coincides with our prolactin findings. We are reproducing his graph (Graph 2).



Graph 2.—Showing the prolactin concentration in a normal healthy woman during the menstrual cycle. (K. Pedersen-Bjergaard.)

SUMMARY

1. The urines of 25 healthy, nonpregnant women were examined daily over a period of two menstrual cycles for the presence of prolactin according to the Visser-Bowman test, Method A.

2. Most of these specimens showed the presence of at least 4 R. U. of prolactin some time during the cycle. The largest number of positive results (49 per cent) was obtained during the second day of the flow, and another peak appeared on the tenth day (36 per cent).

3. From the tenth day to the end of the cycle, the tendency to positive reactions gradually decreased.

4. The Visser-Bowman test was positive in 72.1 per cent and negative in 27.7 per cent of 104 normal pregnant women examined at various periods of gestation.

5. The above chemical test was positive in 85.7 per cent and negative in 14.3 per cent of 7 ectopic pregnancies.

cover thoroughly the fluctuations which might occur. Some authors (Kochmann, 1926; Anselmino, 1934) suggest that the basal metabolism is raised by some ovarian hormone other than estrin.

The vast number of drugs that have been used in the past for the relief of menopausal symptoms is good proof that none has been quite satisfactory.

Of the lot, the bromides have undoubtedly been the most used (King, 1928). Substitutive therapy with the follicular hormone has added greatly to our armamentarium. Prophylactic doses, started at the very onset of amenorrhea, are more satisfactory than attempts to cure symptoms once firmly established. The dose should be the minimum necessary to obtain results. Often 40 R.U. per day of injected amniotin or progynon will suffice (Severinghaus, 1935); even in severe melancholia 600 R.U. per day by mouth generally causes marked improvement (Werner, 1932). Severe cases of menopausal disturbance require long and intensive treatment. Most of the reported failures occurred because too small doses were used or the treatment was not continued long enough.

A true evaluation of the clinical effects obtained by using any therapeutic agent to help castrate women is difficult, because we have no scientific measure for such subjective sensations as nervousness, or even for accurate evaluation of the intensity of the more objective hot flashes.

METHOD

The metabolism tests were made in a basement room of the Department of Biology at Mather College. Rubber-stripped double doors kept out corridor noises, and the adjoining offices were under our control. The apparatus used was a Krogh spirometer. Consecutive tests on the same day with this apparatus and with the Haldane differ by less than 2 c.c. O₂ per minute. A ten-minute test was run after a preliminary rest period of twenty-five minutes. Pulse and temperature were taken immediately after the test. The tests were generally run six days a week; before, during, and after medication. The doses were given twelve to twenty-three hours before observation. With most of the subjects, 5 to 10 basal metabolisms were run before medication to establish their initial level, which was then compared with the Harris-Benedict standard.

Our first four patients were secured through private physicians who generally administered the doses. The next four were obtained from the Gynecological Clinic of Lakeside Hospital through the kindness of Dr. W. H. Weir, and were under the care of Dr. Joseph T. Smith.

The hormone preparations shown in Table I were used.

TABLE I*

NAME	POTENCY PER C.C.	MANUFACTURER
Aqueous theelin	50 R.U.	Parke, Davis & Co.
Oil theelin	1,000 I.U.	Parke, Davis & Co.
Aqueous menformon	100 M.U.	N. V. Organon
Oil menformon	2,500 M.U.	N. V. Organon
Oil amniotin ampules	2,000 I.U.	Squibb
Oil amniotin capsules	1,000 I.U.	Squibb
Thestel capsules	1,000 I.U.	Parke, Davis & Co.

*We are indebted to Dr. Oliver Kamm of the Parke, Davis & Co. for 18 ampules of oil theelin, and to Professor Arthur H. Bill of the Department of Obstetrics and Gynecology for all of the amniotin and thestel and for most of the remaining oil theelin used. We also wish to thank the American Medical Association for a grant in partial payment of other expenses.

THE EFFECT OF ESTRIN UPON THE BASAL METABOLISM RATE AND THE NERVOUS SYMPTOMS OF OVARIECTOMIZED WOMEN*

MARY E. COLLETT, PH.D., JOSEPH T. SMITH, M.D., AND
GRACE E. WERTENBERGER, M.Sc., CLEVELAND, OHIO

WITH THE COLLABORATION OF DRs. D. M. HARLOR, FAITH W. REED,
AND SARA J. LONG

(From the Departments of Biology and Gynecology, Western Reserve University)

INTRODUCTION

IT HAS been known for some time that the basal metabolism of normal women shows a definite monthly variation (reviewed by Hitchcock and Wardwell, 1929). Since the highest metabolism is usually observed in the week before and the week after the menstrual period, times when the corpus luteum and the follicle appear to be very active, it seems possible that the rise in metabolism is due to the secretions of these glands. In order to test this hypothesis we have studied the basal metabolism of ovariectomized women before and after the administration of estrin. If a consistent change should be observed in the basal metabolism after medication, an objective test of the activity of such preparations would then be available, to supplement the clinical evidence of effectiveness. We have also hoped to gain some understanding of the mechanism by which estrin acts.

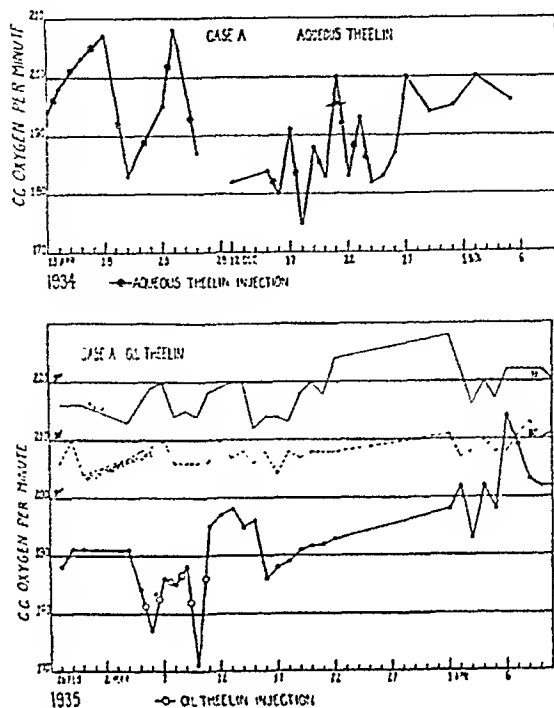
In support of the hypothesis that the basal metabolic rate is affected by the ovarian hormones we already have evidence that women with faulty ovarian function are likely to have a low basal rate.

(Litzenberg, 1929; Randall, 1934; Thurman and Thompson, 1930.) Furthermore, bilaterally ovariectomized women usually have a basal metabolism 7 to 20 per cent below the standard (Allen, 1932). King (1926), however, in a large series of cases, found the basal rate of such women close to the normal level. Further observations on this point would seem desirable.

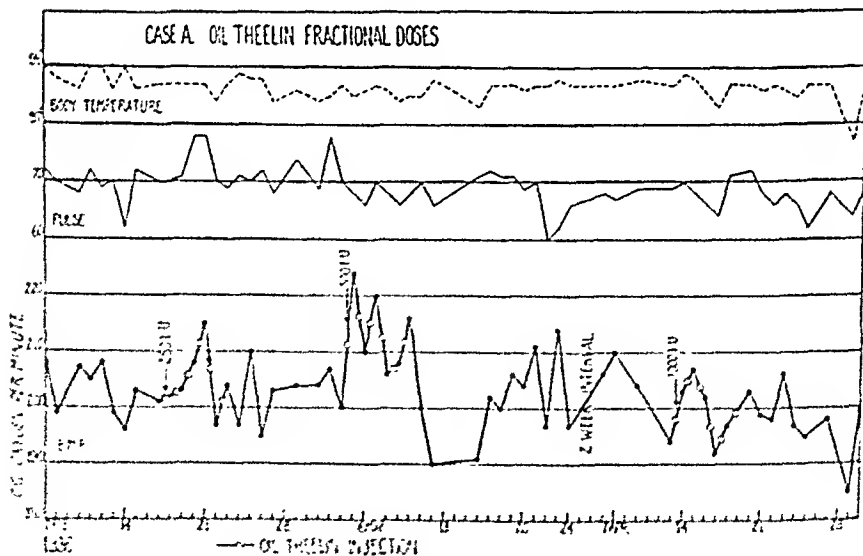
The literature covering the effect of estrin upon the basal metabolism (reviewed by Allen, 1932; Zondek, 1930; v. Arvey and Meyer, 1932) is somewhat confused. The observations cover a great variety of preparations and dosages, but are generally limited to one or two tests before and after medication, and seem to include few consecutive tests, at least on women. Most of the experiments on animals, and rather more than half of those on women, show a rise in basal metabolism after medication; the remainder show a fall or no significant change. In the human cases in which observations were made consecutively over long periods of time (Brugsch and Rothmann, 1926; Zondek, 1930), the general trend is toward a higher level after medication, but in no case have we found daily observations on women such as would

*Aided by a grant from the Council on Pharmacy of the American Medical Association.

The effect of 2 series of 6 injections of aqueous theelin (50 R.U. each), the first covering fifteen days, and the second nine days, was a slight stimulation of the basal metabolism, the second series of more intensive dosage giving the greater rise (Table V and Graph 1). In the latter series we followed the basal metabolism



Graph 1.



Graph 2.

rate for three weeks after medication and found that the greatest rise (plus 8 per cent) came in the second week. The range of variation was much greater than that observed during the control period.

Consecutive injections of oil theelin (1,000 I.U. per dose for six days) produced a fall to -4 per cent during the period of medication, with a gradual rise through the ensuing weeks to a peak of plus 8 per cent in the fifth week and then a gradual

RESULTS

CASE A.—White woman operated upon at thirty-two years of age, twenty-one months before the beginning of our experiments. She was in good health during the experimental periods except for the vasomotor disturbances characteristic of the menopause. In a series of tests made in connection with another problem at twenty-nine years of age, her metabolism was normal, plus 0.6 per cent by the Harris-Benedict Standard. Twenty-one months after operation the basal metabolism had fallen to -13.5 per cent. During the next two years it varied from -20.8 per cent to -13.1 per cent (Table II). The absence of marked daily fluctuations considered as normal even in trained subjects is worthy of note. In the first control period, whose maximum variation was 9 per cent, 8 of the 14 tests varied less than 3 per cent and 4 consecutive tests were identical. In a longer control period of 20 tests one year later, the maximum variation was 8 per cent with half of the tests within a range of 4 per cent. In the next control period eleven months later, the maximum spread was 5.9 per cent with 7 of the 8 tests less than 4 per cent apart (Table III and Graphs 1 and 2).

TABLE II. BASAL METABOLISM RATE DURING CONTROL PERIODS BEFORE MEDICATION

CASE	RACE	HISTORY	TIME SINCE OPERATION	AGE	WEIGHT IN POUNDS	DATE	BASAL METABOLISM RATE IN C.C. O ₂ PER MIN.	PER CENT OF H-B STANDARD
A	W	Op.*	21 months	34	180	10/33	200	-13.5
A	W	Op.	27 months	34	180	4/34	198	-12.5
A	W	Op.	33 months	35	180	10/34	182	-20.0
A	W	Op.	36 months	35	176	3/35	191	-15.0
A	W	Op.	48 months	36	186	2/36	203	-13.1
B	W	X-ray	2 years	29	113	4/34	155	-18.0
C	W	Op.	4 years	31	115	8/34	150	-20.0
C	W	Op.	4 years	31	120	10/34	160	-18.0
D	W	Radium	8 years	42	125	2/35	182	- 5.0
E	C	Op.	3 months	25	121	5/35	157	-20.0
E	C	Op.	7 months	25	130	9/35	157	-22.5
F	C	Op.	3 months	30	137	5/35	154	-21.0
G	C	Op.	9 months	42	132	10/35	167	-15.0
G	C	Op.	14 months	42	132	4/36	167	-15.0
H	C	Op.	9 months	40	176	5/36	194	-11.8

*Op., uterus and both ovaries removed surgically.

TABLE III. RANGE OF VARIATION IN BASAL METABOLISM RATE DURING CONTROL PERIODS, IN C.C. O₂ PER MINUTE

CASE	OBS.	RANGE	DIFF.	AVERAGE	PER CENT MAX. SPREAD
A	14	190-208	18	200	9.0
	3	194-201	7	198	3.5
	6	177-184	7	182	3.8
	20	183-199	16	191	8.3
	8	196-208	12	203	5.9
B	3	155-156	1	156	7.0
C	2	145-155	10	150	6.6
C	2	160-160	0	160	0.0
D	5	180-192	12	181	6.6
E	9	146-158	12	155	7.6
E	6	155-167	12	159	7.6
F	5	148-160	12	155	7.6
G	6	165-173	8	168	5.8
G	7	161-172	11	166	6.6
H	9	189-198	9	194	4.6

TABLE V. BASAL METABOLISM RATE IN PERCENTAGE OF INITIAL LEVEL AFTER CONSECUTIVE DOSES OF THIELIN, AMNIOTIN, THIELOL.

CASE	PREP.	INTERVAL AND TOTAL DOSAGE IU	RANGE					AVERAGE							
			DURING	AFTER MEDICATION				DURING	AFTER MEDICATION						
				1 WK.	2 WK.	3 WK.	4 WK.		5 WK.	1 WK.	2 WK.	3 WK.	4 WK.	5 WK.	
A	Ag. T. EXP. I	6 in 15 da 300 RU	94-105						101						
A	C.L.	6 in 12 da	90-106						100						
A	Ag. T. EXP. II	6 in 9 da 300 RU	96-110	100-108	99-117	98-110			102	104	108	104			
A	O.T.	6 in 6 da 1500 IU	97-102	96-103	98-102				100	99	100				
A	O.T.	6 in 6 da 3000 IU	101-110	93-99	97-105			95-103	105	97	100				102
A	O.T. EXP. I (inj.)	6 in 6 da 6000 IU	89-102	93-103	100-101		101-112	105-112	96	100	100		105		108
A	O.T. EXP. II	6 in 6 da 6000 IU	94-102	96-101	91-98	8 wk. 98-101			98	98	94				
C	O.T.	9 in 10 da 9000 IU	102-114	97-110			97-102		106	104				99	
E	O.T.	6 in 6 da 6000 IU	89-107	101-108	98-105	98-105	98-106		97	104	101	101			
F	O.T.	6 in 6 da 6000 IU	86-102	103-111	102-115	106-120	106-116		96	106	106	116		113	
E	O.A. oral	20 in 20 da 20,000 IU	98-113	108-115	102-117	113-118	108-109		108	112	111	115		109	
G	O.A. oral	20 in 20 da 20,000 IU	95-114	98-118	91-112	102-114	105-111	109-111	105	106	105	108		108	111
G	O.A. oral	20 in 20 da 20,000 IU	87-107	87-102	90-100	94-104	93-112	96-100	97	95	95	100		102	97
H	O.A. oral	20 in 20 da 20,000 IU	95-106	93-106	89-116	96-103	92-119	98-99	100	99	100	100		101	98
G	Theodol. oral	18 in 18 da 18,000 IU	89-118	94-105	96-107	87-100	100-100		102	100	100	95			

fall, until by the eighth week the initial level was reached. Again the range of variation was greatly increased during medication and during the following weeks while the effect of the injections lasted, but gradually returned to normal by the eighth week (Table V and Graph 1).

TABLE IV. BASAL METABOLISM RATE IN PERCENTAGE OF INITIAL LEVEL, AFTER SINGLE INJECTIONS OF THEELIN OR AMNIOTIN

CASE	RANGE	OIL THEELIN			CASE	RANGE	OIL AMNIOTIN		
		% DIFF.	4-DAY AV.	DOSE			% DIFF.	4-DAY AV.	DOSE
C	99-115	16	113	1000 I.U.					
	99-115	16	110	1000 I.U.					
	99-107	8	97	1000 I.U.					
D	93-101	8	94	1000 I.U.					
	85-90	5	90	1000 I.U.					
	92-99	7	95	1000 I.U.					
	94-102	8	98	1000 I.U.					
	92-98	6	95	1000 I.U.					
	90-94	4	92	1000 I.U.					
E	91-100	9	95	1000 I.U.	E	93-109	16	99	1000 I.U.
						98-109	11	103	2000 I.U.
						102-114	12	107	2000 I.U.
F	93-105	12	100	1000 I.U.	F	97-109	12	102	1000 I.U.
						101-110	9	107	2000 I.U.
G	96-106	10	103	1000 I.U.	G	86-105	20	97	2000 I.U.

A series of graduated doses of oil theelin was given Case A in order to study the quantitative relation of dosage to basal metabolism rate (Table V and Graph 2). Six one-fourth cubic centimeter doses on six consecutive days (1,500 I.U.) had no effect on the average basal metabolism rate through the period of medication nor in the following week. A second series of 6 one-half c.c. doses covering six days produced a rise of 5 per cent in the average basal metabolism rate during the period of medication and a fall to -3 per cent in the week following the injections. A two-week interval occurred at this point, and when tests were resumed, the basal metabolism rate had risen to plus 2 per cent. The last series of injections consisted of 1 c.c. doses on six consecutive days and the basal metabolism rate fell to -2 per cent during medication and to -6 per cent two weeks later. The maximum variation during the first series did not exceed that observed during the control period. The next two series, however, produced the marked daily fluctuation and the increased range of variation previously noted after estrin medication. The observations should have been continued for at least two weeks longer in order to determine the full effect of the medication. This series is especially significant because it shows both stimulation and inhibition of the basal metabolism rate by estrin.

Menformon injections totaling 7,200 M.U. in six days also raised the basal metabolism rate of Case A by 6.6 per cent during the period of medication, and, as in the case of theelin, produced a wider range of variation.

A day-to-day record of the number of hot flashes was not kept for Case A, but marked changes were noted. The hot flashes, which began in the third week after operation, were frequent and severe. A series of aqueous theelin injections did not alleviate them. The first relief was secured after a series of aqueous theelin followed by corpus luteum injections, but the effect was short-lived. We have generally observed that days of high basal metabolism rate after estrin medication are days of few vasomotor symptoms, but the rise in basal metabolism rate per se does not seem to be the only factor involved, for after thyroid medication the basal metabolism rate rose by 24 per cent and the vasomotor symptoms increased. Thyroid medica-

metabolism rate two years after operation was -18 per cent. She received 1 c.c. of oil theelin every seven to ten days, and responded by rise of 8 per cent in basal metabolism rate. Although some ovarian function remained, it is interesting to note that each theelin injection was followed by an immediate cessation of the hot flashes and the sense of fatigue, an improvement which lasted for about a week and paralleled the period of increased metabolism. This case was interesting as one of inadequate ovarian function, but was unsatisfactory since the amount of ovarian activity was quite uncertain, and the case was not available for daily observation.

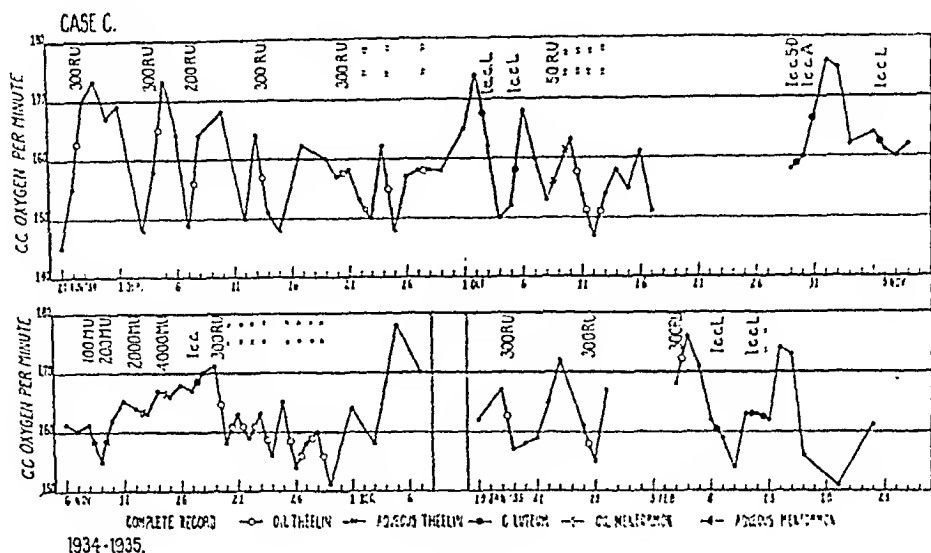
CASE C.—A white woman operated upon at twenty-seven years of age. Her basal metabolism rate before medication, four years after operation, was -20 per cent (Table II). The entire history of her estrin medication is shown in Graph 3. She responded to single 1 c.c. doses of oil theelin (Table IV) by a rise in basal metabolism rate of 7 to 15 per cent, the variation depending apparently upon the frequency with which the doses were given. Table V shows the effect of a series of consecutive doses of oil theelin, with a range of 16 per cent and an increase of 6 per cent in the average basal metabolism rate during medication. This wide range of variation persisted and the average level remained at plus 4 per cent during the week following medication. Menformon injections totaling 2,300 M.U. produced a rise of 10 per cent in the average basal metabolism rate, and marked daily fluctuation.

This patient before the beginning of medication looked much older than her years and showed the marked instability characteristic of these patients. After each dose of theelin her face looked fuller and more youthful, and the skin less drawn. She complained of sleeplessness, fatigue, and nervousness as well as of hot flashes, which varied in number and intensity from day to day. The first three injections of oil theelin were followed by slight improvement in the insomnia, but the hot flashes and other symptoms persisted. With 1 c.c. of oil theelin every other day for four doses, hot flashes became much less noticeable during the medication, and were not troublesome for three weeks. Small doses ($1/6$ c.c.) of oil theelin given on three successive days caused no change in the hot flashes, although the insomnia and nervousness were better. On resuming the tests after a month without medication, the patient was having numerous hot flashes. An intensive series of theelin injections (1 c.c. daily for nine days) was followed by marked improvement in sleep and nervous control, and by remission of the hot flashes for a week. Then they returned, although the basal metabolism rate continued high. After two injections of menformon (200 M.U.) she felt dizzy and uncomfortable. It is interesting to note that after the second dose of menformon there was a distinct odor of menstruation and an increased vaginal discharge, greater than that observed after theelin. Neither this dosage of menformon nor the heavier one which followed benefited the hot flashes.

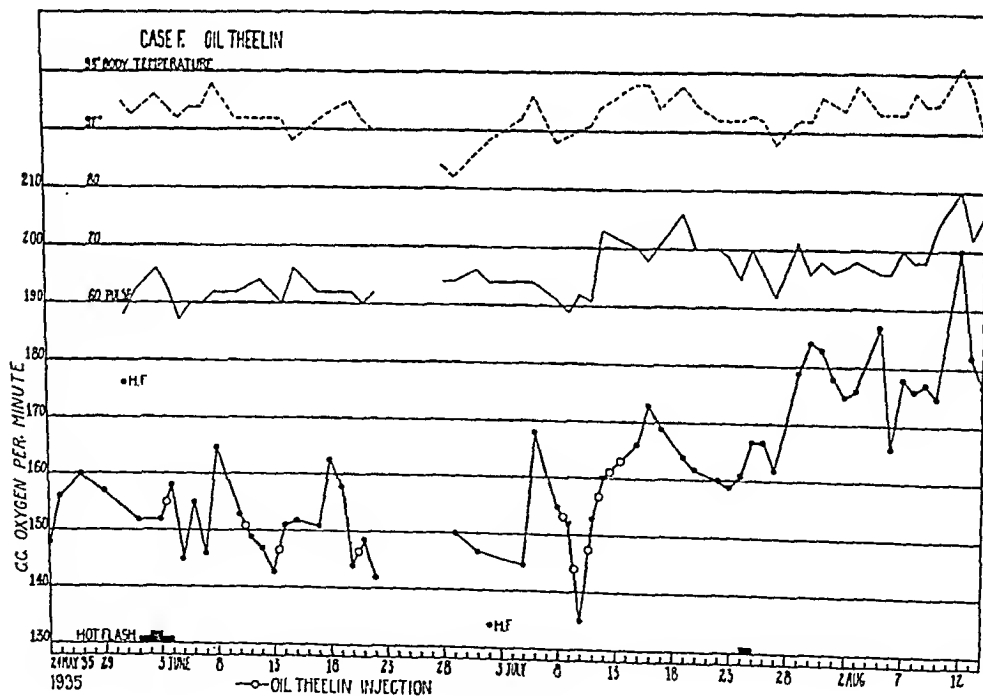
CASE D.—A blind white woman who had received heavy radium treatment for an uterine tumor at thirty-four years of age. Eight years later her basal metabolism rate was -5 per cent (Table II). She received eight weekly doses of 1 c.c. of oil theelin. After each dose her basal metabolism rate fell from 5 to 8 per cent for a few days (Table IV). The hot flashes were intensified for a day or so after each dose except the last. At the conclusion of the course of treatment the patient was no longer tired, nervous, and depressed, but reported that she felt "fine."

CASE E.—A colored woman operated upon at twenty-five years of age. She was in good health throughout the experiments except for the usual menopausal symptoms. Three months after operation her basal metabolism rate was -20 per cent, and four months later was -18 per cent (Table II). Her metabolisms during the initial period were remarkably steady: 7 out of 9 tests in one series varied by less than 1 per cent, and 4 out of 6 in another series were identical (Table III and Graphs 5

tion has repeatedly had this effect upon Case A. During the following year the hot flashes gradually disappeared spontaneously and the patient was free of them for about four months. A series of oil theelin injections begun at this time was accompanied by a sharp return of both hot flashes and headaches. As the dosage continued, these gradually faded and became almost negligible three weeks after med-



Graph 3.



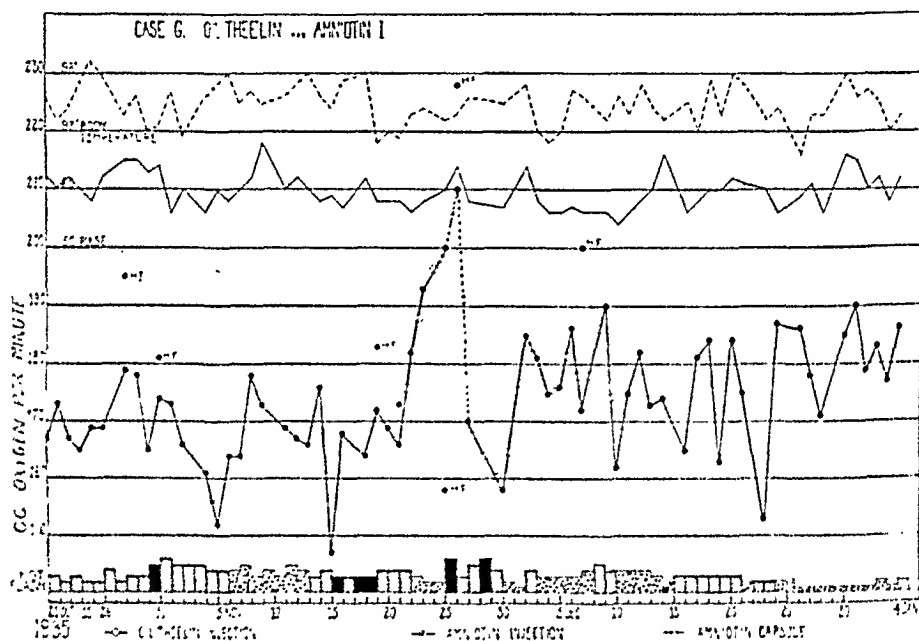
Graph 4.

ication. Insomnia and general nervousness responded better to oil than to aqueous preparations. Since a prolonged effect is desired the oil preparations with their slower rate of absorption have a distinct advantage.

CASE B.—Patient received x-ray treatment at twenty-seven years of age for excessive bleeding, and menstruation ceased for eighteen months; it then reappeared but was scanty and irregular until theelin administration was begun. Her basal

The average basal metabolism rate following the amniotin was greatly increased and remained high for four weeks, with the greatest rise in the third week.

Beginning with Case E a daily record was made of the number and intensity of the hot flashes (Graphs 5 and 6). The injections of oil theelin given to Case E at three- to five-day intervals after June 3 were followed by a definite reduction in the number and severity of the hot flashes, paralleling a rising basal metabolism rate. Then [as though such small doses required cumulative storage to be effective] the basal metabolism dropped sharply, accompanied by a marked rise in the number and intensity of the hot flashes and in nervousness. The intensive series of daily injections for a week, starting July 8, may have given better cumulative storage, for after three doses the basal metabolism rate was rising, the hot flashes were decreasing, and the patient was feeling much better. This improved platform was maintained for about twelve days after the injections ceased. Then the basal level dropped and the flashes became more marked. Three scattered injections of amniotin in September (totaling 5,000 I.U.) were followed by a good rise in the

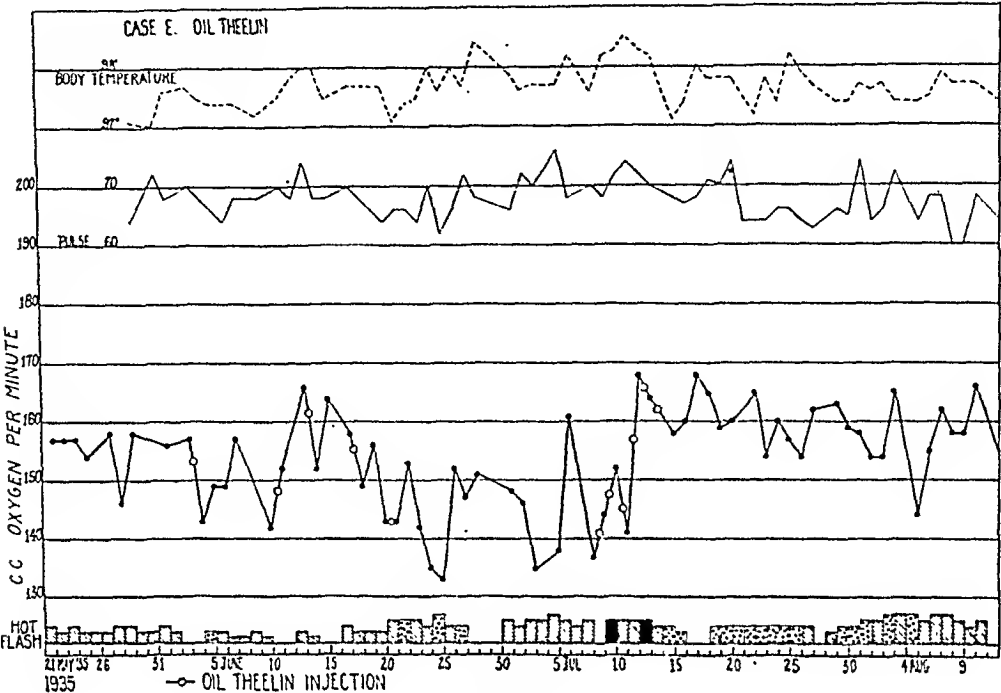


Graph 7.

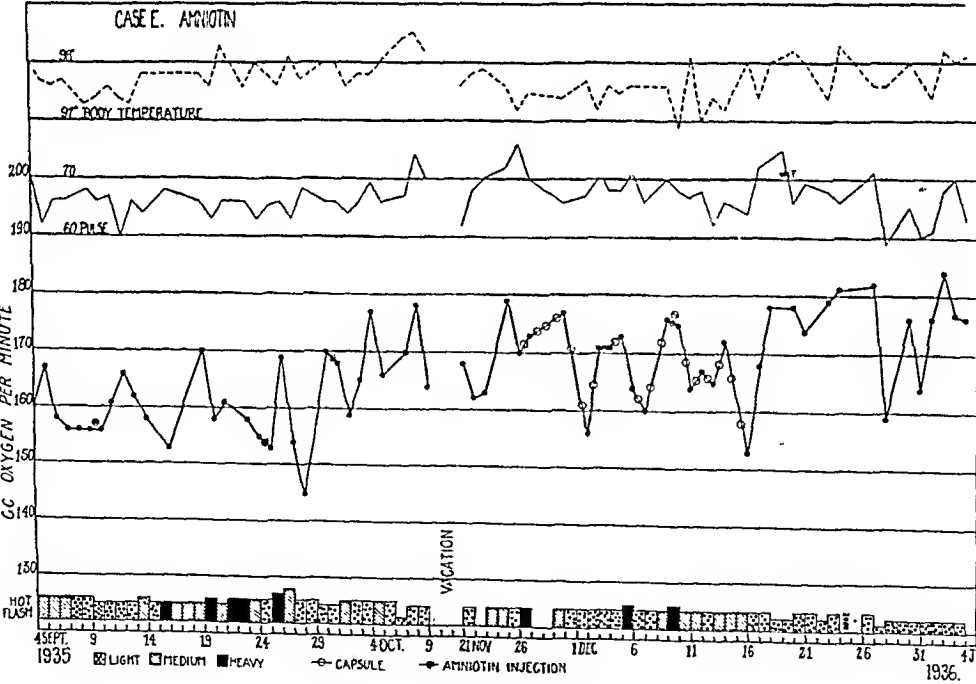
basal metabolism rate and a synchronous fall in the hot flashes. The most striking clinical picture shown by this patient was the condition following the daily use of amniotin capsules. During the twenty days of their administration, the basal metabolism ran an irregular course and the hot flashes showed little change in number or intensity, though possibly a slight decrease. With this cumulative mass of amniotin in the system, however, the metabolism rose well above the initial level and the hot flashes were markedly decreased. This improvement persisted for over three months, much longer than after the series of injections.

CASE F.—A colored woman operated upon at thirty years of age. Three months later she had a basal metabolism rate of -21 per cent (Table II). During the control period four out of six determinations were less than 2 per cent apart (Table III and Graph 4). She was a frail woman who had to be watched constantly for minor infection. Experiments had finally to be discontinued because a mild hypertension and low-grade nephritis developed. Her basal metabolism rate showed the usual increased variation after single 1 c.c. doses of oil theelin (Table IV), but the average level was not affected. She responded like Case E to consecutive doses of oil

and 6). Table IV shows the effect of single doses of oil theelin and oil amniotin, which closely resembles that observed in our previous cases. Table V shows the effect of consecutive doses. During the administration of a course of oil theelin and



Graph 5.

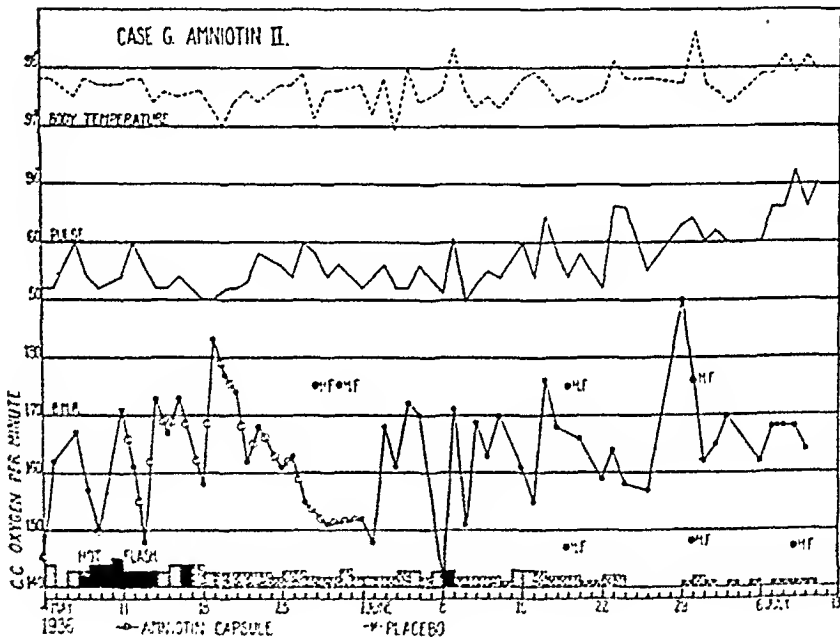


Graph 6.

for four weeks afterward, the range of variation was greatly increased over that of her control period. The average level was -3 per cent during medication and rose to plus 4 per cent in the following week; in the succeeding three weeks it returned to normal. During the oral administration of oil amniotin, the range was again wide.

mouth (1,800 I.U. in eighteen days). There was only a slight rise during medication; then the average level returned to normal and fell during the third week to -5 per cent. The range of variation was greater than at any other time, reaching 29 per cent during medication and continuing at about 12 per cent during the next three weeks. A placebo (1 c.c. injection of sterile sesame oil) which was given six weeks after the last dose of amniotin had no effect upon the basal metabolism rate; the tests on the day preceding the injection and on the two following days were identical, and the hot flashes showed no change.

Case G seems to affirm the idea of the prolonged beneficial effect of intensive oral administration of some preparations of estrin (Graphs 7, 8, 9). After 1 injection of oil theelin, an increase in hot flashes coincided with a fall in metabolism. One injection of oil amniotin (1,000 I.U.) was followed by a rise in basal metabolism rate and a subsequent decrease in hot flashes which persisted for ten days. After oral administration was begun, there was a period when hot flashes were severe and frequent; then the hormones seemed to get control, and while the basal metabolism rate



Graph 9.

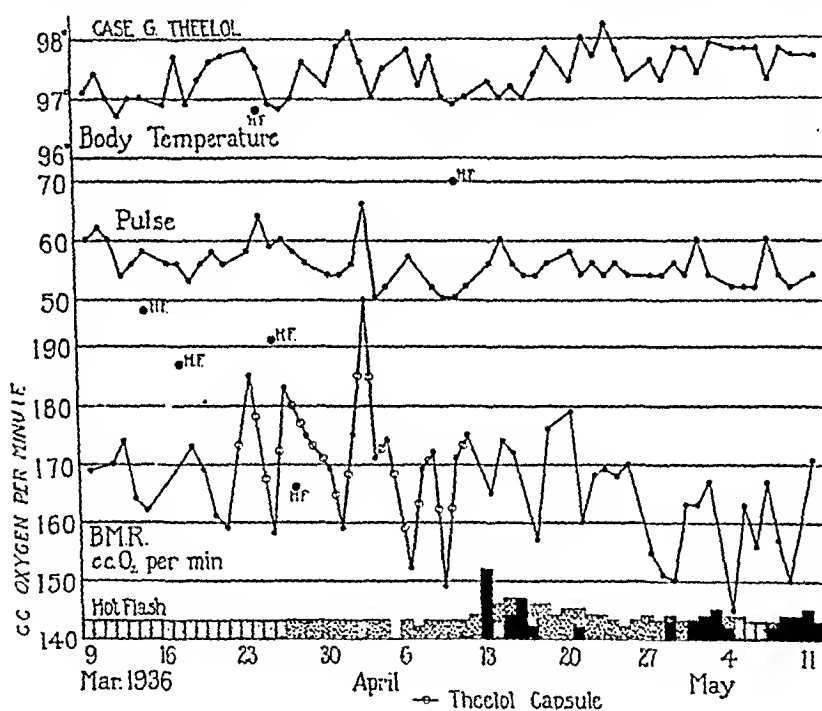
was held at a higher level the hot flashes were at a minimum for fully thirty days. The improvement lasted for about two months. In the third month the hot flashes became more annoying. Late in February there were occasional heavy ones, and in early March they were averaging three of medium intensity per day. During the daily administration of theelin capsules, begun at this time, the hot flashes became much lighter and the basal metabolism rate fluctuated widely. For a week after the last capsule they were once more heavy and numerous and then for a fortnight became very light again. The use of theelin capsules was helpful but seemed to be less effective than amniotin by mouth (Graph 8). In order to see how much of this was due to a difference in the preparations and how much to season, or to the patient's condition, a second series of amniotin capsules was given in May and June.

When the second series of amniotin capsules was begun, the hot flashes were frequent and heavy (Graph 9). By the third week of medication they had begun to decrease in number and intensity. This improvement proceeded until in the fourth week she was reporting only one or two very light hot flashes a day. In the fifth week she reported two days with no flashes and on the other days only one. In general

theelin (Table V) except for the fact that the rise in the third and fourth weeks was unusually great, perhaps because of the hypertension which developed at that time.

Case F had remarkably few hot flashes of any kind although she was very nervous (Graph 4). Three hot flashes occurred just before the first injection of theelin. There was one hot flash after the first injection and then none for six weeks, in spite of the fact that the metabolism at times fell very low. Some of these depressions were due to slight physical upsets. At the conclusion of the series, when the basal level was falling steadily, she had one severe hot flash.

CASE G.—A colored woman operated upon at forty-one years of age. Nine months and again fourteen months later her basal metabolism rate was -15 per cent. During the first control period five out of six determinations were less than 2 per cent apart and in a second series five out of eight were less than 2 per cent apart (Tables II and



Graph 8.

III and Graphs 7 and 8). Single doses of oil theelin and oil amniotin (Table IV) in this as in the other cases induced wide variation in basal metabolism rate; the average rose slightly after theelin and fell slightly after the more potent amniotin.

A course of oil amniotin by mouth (1,000 I.U. daily for twenty days) administered in the winter gave results which are comparable with Case E (Table V and Graph 7). There was a rise in the average basal metabolism rate during the period of medication and this persisted with some variation during the succeeding five weeks, reaching its peak in the fifth week. Again the range of variation was greatly increased. A second series in the summer of the same year, however, showed a slight depression in the average basal metabolism rate with a gradual return to the initial level, and a slight rise in the fourth week. Excessively hot weather which occurred at this time may have been a complicating factor, for in the next week the basal metabolism rate again fell. But, as with theelin in the other cases and amniotin in Case E, the range of variation was great, varying from 12 to 20 per cent during the two series as compared with a maximum spread of 6 per cent in the control periods. Between the two amniotin series the patient was given a course of theelin by

disappear, the dosage used seems to have been too light. A second series with increased dosage should be tried to determine if possible the cause of this refractory condition.

We have made a few observations upon hot flashes occurring during the metabolism tests. Respiration is irregular in rate and in depth; inspiration is usually deep and expiration is often incomplete. The pulse is rapid. The metabolism is increased by 5 per cent or more in severe hot flashes and may not return to normal for ten or fifteen minutes. The hot flashes are generally followed by sweating. Several of the patients described the sensation as one of sudden, intense skin hotness, with a pounding heart and a terrifying feeling of suffocation. They sometimes stiffen visibly during a hot flash.

Pulse and body temperature changes in general parallel the changes in basal metabolism rate, though the parallelism is not absolute. Pulse tends to show a greater fluctuation than body temperature, the latter lagging a little behind the changes in basal metabolism rate. The maximum variations in both come during the period of greatest variation in the basal metabolism rate.

DISCUSSION

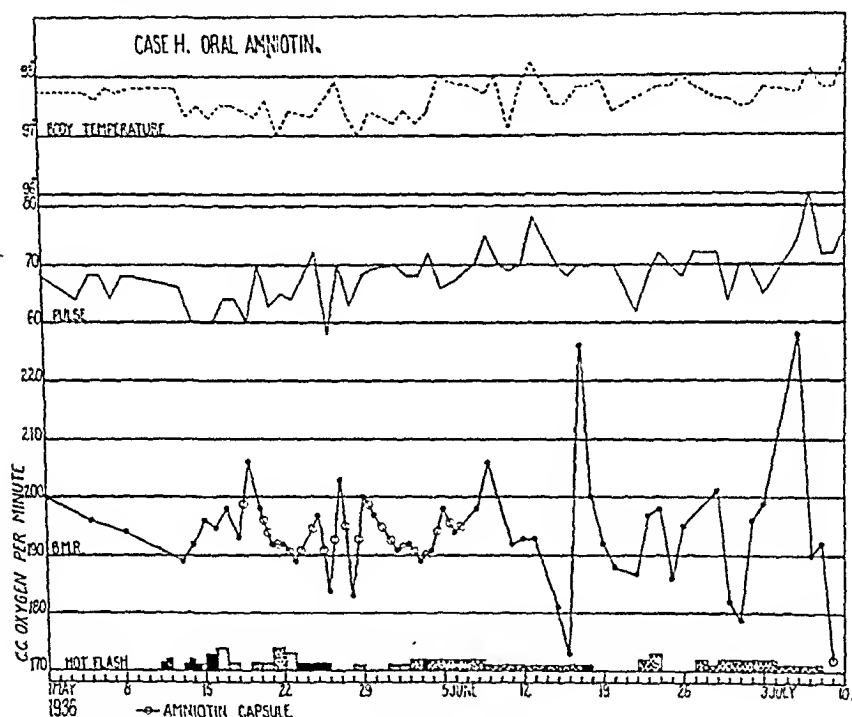
Our observations agree with most of those previously reported in indicating that the basal metabolism rate is lowered by castration. With the exception of Case D, whose blindness was a complicating factor, we found the basal metabolism rate from 12 to 20 per cent below the normal (Harris-Benedict). We are thus far unable to corroborate King's observations.

The steady metabolic level of our cases before estrin administration is striking. The maximum spread of consecutive daily tests before medication is only 8 per cent, and few of the tests were more than 2 per cent apart. This is much less than the usual spread regarded as within the normal range clinically (25 per cent), and is also less than the monthly fluctuation of trained normal women, which amounts to 10 to 15 per cent. The steadiness of our cases is important in evaluating the significance of the variation observed after medication.

The average basal metabolism rate in the first four days after 1000 I.U. of oil theelin or amniotin, by injection, is not very different from the average level before, but the variation is greater, 7 to 16 per cent as compared with 1 to 8 per cent. Consecutive doses of injected theelin or of amniotin by mouth are generally followed by a wide variation and by a fall in the average level during medication, which is succeeded by a compensatory rise in the following weeks. Great variation is also observed after theelin by mouth. Such a range of variation as we have found after medication would perhaps not be significant if we were dealing with casual clinical observations. But when such variation

higher levels of the basal metabolism rate accompanied this improvement. She also reported in the third week of medication that she "felt fine and didn't feel tired any more; that sluggish feeling was all gone." Her mental attitude was cheerful and interested and she seemed to have a great deal of energy. She said she felt better on this medicine than on the other (theelol). Though this series did not show the marked rise in average basal metabolism rate observed in the first series, the subject seemed to feel the same improvement in general well-being. The rapid fading of the effect of theelol both on basal metabolism rate and on the vasomotor symptoms as compared with the prolonged effect of amniotin is worthy of note.

CASE H.—A colored woman operated upon at thirty-nine years of age. Nine months later her basal metabolism rate was -11.8 per cent (Table II). It showed the small range of variation noted in the other cases, with 7 out of 9 tests 2.5 per cent apart and a maximum variation 4.6 per cent (Table III and Graph 10). A series of



Graph 10.

oil amniotin by mouth (1,000 I.U. daily for twenty days) had practically no effect on the average basal level. The range of variation, however, was wide, from 11 per cent during medication to 27 per cent in the second and fourth weeks after medication. The very hot weather which occurred in the latter part of this experiment may have been a complicating factor.

Case H was a large woman with a listless, apathetic manner, who gave a history of frequent severe headaches, heavy hot flashes, chronic constipation, and severe muscle cramps and numbness of the right hand. Beginning with the last week of medication and continuing throughout the next five weeks, the hot flashes were much lighter and she had no recurrence of the muscle cramps. Her first headache occurred in the fifth week. She moved about with more energy and her mental and emotional attitude seemed greatly improved. The digestive condition had cleared up to a great extent but this may have been due to improved eating habits, regular sleep, and a more carefully regulated diet, rather than to the medication. Since the basal metabolism rate showed no significant response and the hot flashes did not completely

uterus sensitized to pitocin by the presence of estrin. We cannot accept this idea, at least for human beings, in view of our results, although it is possible that the smooth muscle of the intestine may be sensitized in this fashion.

The bulk of the experimental evidence points to the anterior pituitary as an intermediary because of its thyrotropic action. The reciprocal influence of anterior pituitary and gonads upon each other has often been demonstrated in regard to the gonadotropic hormone. Moore and Price (1932) found the secretion of both gonadotropic and growth hormones inhibited by estrin. Lane (1935) found that small estrin injections stimulate, while heavier dosages inhibit, the production of gonadotropic hormone. This inhibition under heavy estrin dosage is explained by Halpern and d'Amour (1936) as being due to an overstimulation of the pituitary which brings about a period of overgrowth at the expense of secretory activity.

The close relationship existing between the pituitary and the thyroid has been clearly established both experimentally and clinically.

Kippen and Loeb (1936) found that histologic evidence of thyroid stimulation occurred during the first week after gonadectomy, but that this effect soon disappeared and thyroid activity then fell below normal. Andersen and Kennedy (1933) have described an atrophy of the adrenal and the thyroid after ovariectomy, and a temporary increase in pituitary weight. Conklin and McClendon (1930) found in the menstrual cycle a rise in basal metabolism rate of six times the probable error at the time in the cycle when according to Frank the concentration of the follicular hormone was highest in the blood. Sherwood and Bowers (1936) working with rats, and Starr and Patton (1935) working with women, have shown that prolonged estrin administration reduces the basal metabolism rate of hyperthyroidism, and suggest that the effect is by way of the hypophysis.

We seem to be dealing with a specific hormone inhibition, or with a general inhibition of secretory activity exercised by the follicular hormone over the anterior pituitary. If the inhibition is specific, then we must look elsewhere for the effective site; but if it is general, then it seems reasonable to expect that, coincident with fluctuations in pituitary activity due to ovarian control, we have fluctuations of thyroid activity which show in the basal metabolism rate, making allowance for the lag always associated with the thyroid hormone. Whether we are to observe a rise or a fall in basal metabolism rate after estrin will then depend upon the size of the dose and the duration of the treatment.

Zwecker (1936) has shown that the castration cells of the pituitary do not produce the thyrotropic hormone, for special cells appear in several species alongside the castration cells after thyroidectomy. However the thyrotropic cells may be inhibited mechanically by the pressure of the large castration cells in the gonadectomized animal; and this would result in the lower basal metabolism rate actually observed. Or if both thyrotropic and gonadotropic hormones are produced in larger amount after castration, the thyroid atrophy encountered may be an expression of the antithyrotropic effect observed by Collip and his coworkers.

occurs in trained subjects like ours, it cannot be explained as lying within the expected range of chance variation, and is therefore the result of medication. This initial instability of the basal metabolism rate during estrin administration may be due to the same cause as the increased vasomotor instability reported by Whitehouse (1933), that is, an initial increase of irritability of the sympathetic nervous system as evidenced by an aggravation of the vasomotor symptoms with estrin administration when the opposite was expected. Such an effect was noticed in Case A when a series of theelin injections brought a return of hot flashes and headaches which had been absent for four months.

The changes in basal metabolism rate after oral administration of amniotin and theelol offer an objective demonstration of the absorption of estrin through the gut, and show that the clinical improvement reported is not due to suggestion. Animal experiments (Rowe and Simond, 1936) show that about 33 per cent of the potency (as judged by the induction of estrus) is available in theelol given by mouth. Severinghaus (1935) estimates that 20 to 30 per cent is available by this route in women, as judged by the relief of menopausal symptoms.

The five patients receiving single injections of oil theelin reported lessened nervousness and fatigue for several days after medication, and for four to eight weeks after larger doses of injected theelin or orally administered amniotin. During oral administration of theelol a similar improvement was reported but did not last so long. All except Case D also reported improvement in the hot flashes after medication, the extent and duration of relief depending upon dosage. The relief of nervous symptoms generally parallels a rising metabolism but that increased metabolism is not the only factor involved was shown in Case A when a 24 per cent increase in basal metabolism rate brought about by thyroid administration was accompanied by severe vasomotor symptoms. This increased irritability of the sympathetic nervous system was probably an expression of adrenalin hypersensitivity, since it is well known that thyroid hormone sensitizes the body cells to the action of adrenalin (Marine, 1935). It is probable that relief of the nervous symptoms is due to the direct effect of the ovarian hormone upon the adrenals and the pituitary: Hannan's (1928) theory points to action upon the adrenals whose unbalanced behavior resulting from a withdrawal of the ovarian hormone brings about an increased tonus of the sympathetic nervous system.

The mechanism by which estrin affects the basal metabolism rate is not clear. Pratt (1936) suggests a special thyrotropic hormone of the ovary as does Anselmino (1934). Von Arvey (1932) states that in ovariectomized rats the basal metabolism is raised by estrin administration only if the uterus is left intact, and suggests that the increase observed in basal metabolism rate is caused by increased oxidation in a

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STUDIES ON DRIED BLOOD SERUM OF WOMEN

ALFRED M. HELLMAN, M.D., F.A.C.S., AND GEORGE MUSA, M.D.,
NEW YORK, N. Y.

IN THE April, 1936, issue of the *American Journal of Obstetrics and Gynecology*, Joseph T. Smith¹ described a method of examining dried blood serum of women that might aid in evaluating the amounts of circulating hormones in the blood. This method and the results obtained seemed so intriguing that we undertook to make a further study of this problem.

In an earlier paper Bergauer, Boucek, and Podrouzek² had employed the same method in examining dried drops of blood serum of women in the various phases of the menstrual cycle. They had stated that at the end of the menstrual discharge the resultant pictures of the dried serum were composed of circles resembling snowflakes. A few days after menstruation these disappeared completely. During a more or less long period the dried drops did not show any internal organization, being filled with irregularly arranged crystals. The filiform circles again appeared and gradually became definitely outlined with the approach of menstruation. The authors concluded that the blood of women undergoes periodic fluctuations during the intermittent periodic function of the endocrine glands.

In order to be sure about a different endocrine status, we chose to examine such varying blood serums as: premenstrual, intermenstrual, postmenstrual, pregnancy, puerperium, artificial menopause, chorion-epithelioma, and a male control.

We closely followed the technique outlined and used by Smith and Bergauer in diluting the blood with normal saline solution, and we also dried our specimens in the incubator at 37° C. for twenty-four hours. Both Bergauer and Smith pointed out that it is not absolutely necessary to remove the blood corpuscles, but we found that in not doing so

CONCLUSIONS

1. Trained women twenty-five to forty-two years old, ovariectomized and hysterectomized surgically three months to five years before observation, generally showed a basal metabolism rate 12 to 20 per cent below the Harris-Benedict standard.

2. Their basal metabolism rate is very steady, usually fluctuating within 2 per cent of their mean level, and showing an extreme fluctuation of 8 per cent.

3. Estrin, in the form of theelin, theelol, or amniotin, affects the basal metabolism rate decidedly, and if given in sufficient amount raises the level for some time after treatment. Heavy doses produce a fall during administration of the hormone which is succeeded by a rise in the basal metabolism rate.

4. Single doses of oil theelin (1000 I.U.) or oil amniotin (1000 and 2000 I.U.) given intramuscularly are followed by a fluctuation in the basal metabolism rate varying from minus 8 to plus 14 per cent of the initial level, depending apparently upon the glandular balance of the subject.

5. Consecutive doses of these preparations are followed by greater alteration in the basal metabolism rate and give more lasting results than single doses. The range of variation is wide, running in different patients from minus 4 to plus 5 per cent during medication, and from plus 4 to plus 16 per cent after medication.

6. That estrin is effective by mouth is shown by the greatly increased variability of the basal metabolism rate during oral administration of amniotin and theelol although a significant rise does not always result. Clinical improvement is more lasting after amniotin than after theelol.

7. The administration of estrogenic substances in suitable doses is followed by a decrease in the number and intensity of hot flashes, decreased nervousness, and lessened fatigue, synchronizing with a higher basal level. Hot flashes are harder to check than the symptoms. Reappearance of vasomotor symptoms may occur with estrin administration in some cases.

8. Treatments are cumulative; the effect does not begin until several doses have been taken. The effects of oral administration persist longer than if equivalent amounts of the hormones are given by injection over a shorter period.

We are greatly indebted to Professor A. J. Carlson and Professor Torald Sollmann for suggestions as to plan of experiment and to Drs. Eva Lagerwall, William McCann, S. H., and K. K. Chen, for criticism of our manuscript. We also wish to express hearty thanks to our assistants, Miss Margaret Schott, Miss Florence Lawton, and Miss Janet Baughman, who ran about half of the metabolism tests.

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the specimen became very inaccurate and showed a clump of corpuscles in the center of the drop and a thin outer rim of crystallized fluid. In

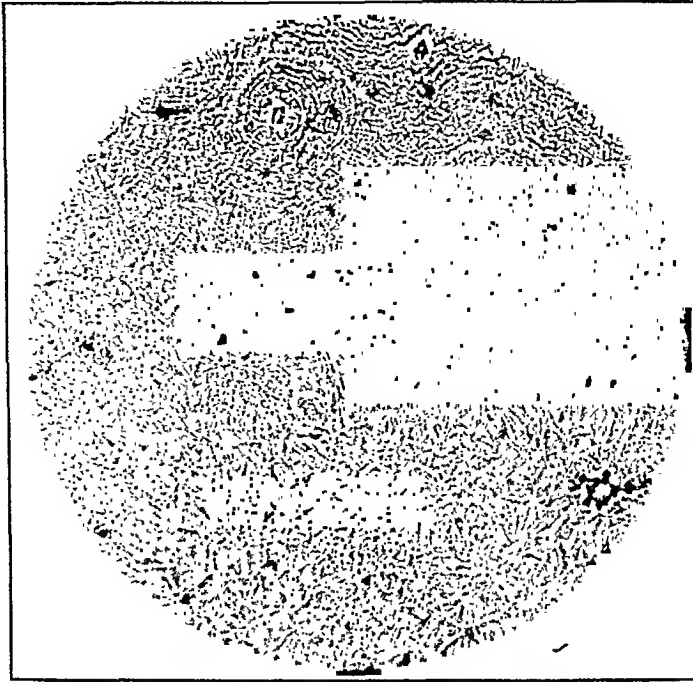


Fig. 1.—Leaf, aster, and ring formation. Premenstrual.

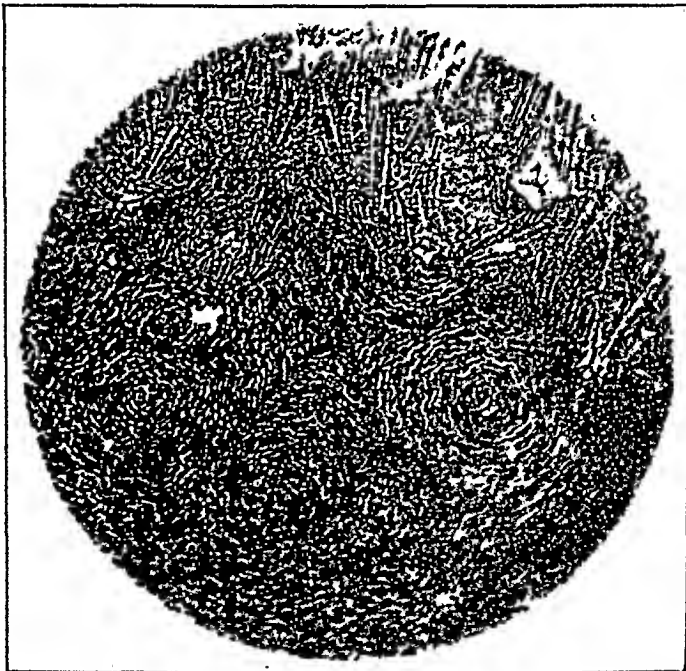


Fig. 2.—Interrupted rings, and "lead-window" formation. Premenstrual.

several tests these forms of crystallization were different from those obtained with centrifuged diluted serum. Therefore, we centrifuged all our serum as did Smith and Bergauer.

TABLE I

FORMATION	POSTMENSTRUAL DAYS				PREGNANCY							ARTY- FICIAL MENO- PAUSE	CHORION- EPITHE- LIONA	PUER- PERTUM	MALE	TOTAL	
					BEFORE DELIVERY	9TH MO.	8TH MO.	7TH MO.	6TH MO.	5TH MO.	3RD MO.						
	1-7	8-14	15-21	22-28													
Iced window		1		1													3
Leaf			1	1	1												3
Asters																	1
Rings (regular)	1	3		1	1	1	1	1	1	1	1	1				1	11
Rings (interrupted)		1															4
Radiant				2	2		1	1	1	1	1	1				1	2
Combined	1												3				11
Total	2	5	3	5	2	1	2	1	1	1	1	1	3	1	5	2	35

phases of the menstrual cycle. The pregnancy serums were more consistent as they primarily showed the ring formation, but this form was also present in one postmenstrual serum, in 3 of 5 puerperal serums, and in one male serum. One pregnancy serum showed the leaf formation and two showed a combined picture of ring and aster formations.

We examined and classified our specimens by the results obtained under low power. We noted that a number of the ring forms when seen under high power resembled the "bastioned" type described by Smith. It, therefore, appears necessary to compare all patterns only under one power of the microscope.

In evaluating the groupings of the different drops it became clear that the pictures were not uniform enough to insure a reliable reading.

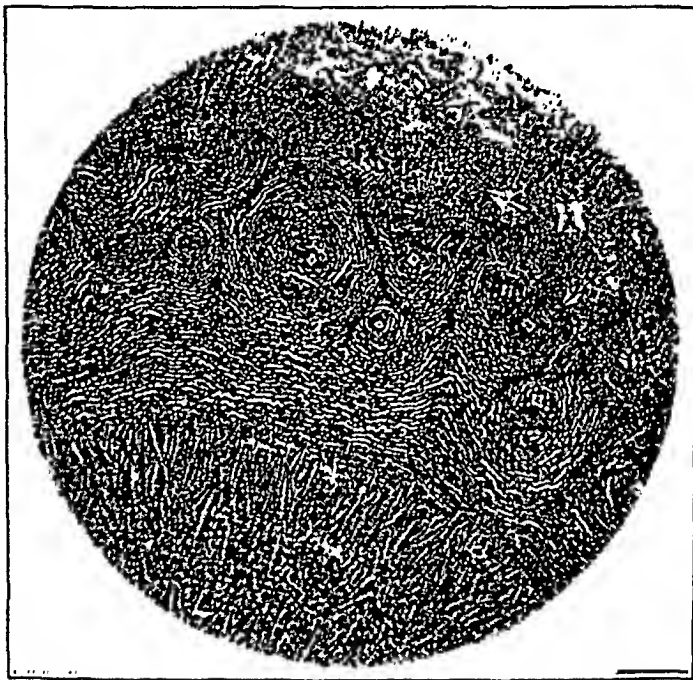


Fig. 5.—"Iced-window," rings, and lines. Artificial menopause.

Very frequently we found a different form of crystallization on the outer edge of the dried drop from that seen in the center. In contrast, other drops showed two or even three different forms of crystallization in the center of the drop. It is evident that the interpretations of such specimens differ with the individual who reads them and are, therefore, a significant source of error. We grouped those cases under the heading "combined" and found 11 such forms among the 35. These combined forms are illustrated by Figs. 1 to 5.

It certainly would be a very welcome aid to our diagnostic technique were we able to get a reflection of the endocrine status in a drop of dried serum of our patient. Were the assumption really true that the difference of the patterns depends upon the endocrine content of the serum, it surely would show itself in the varying endocrine con-

The results of 35 specimens obtained from patients in the wards and Dispensary of Sydenham Hospital are shown in Table I.

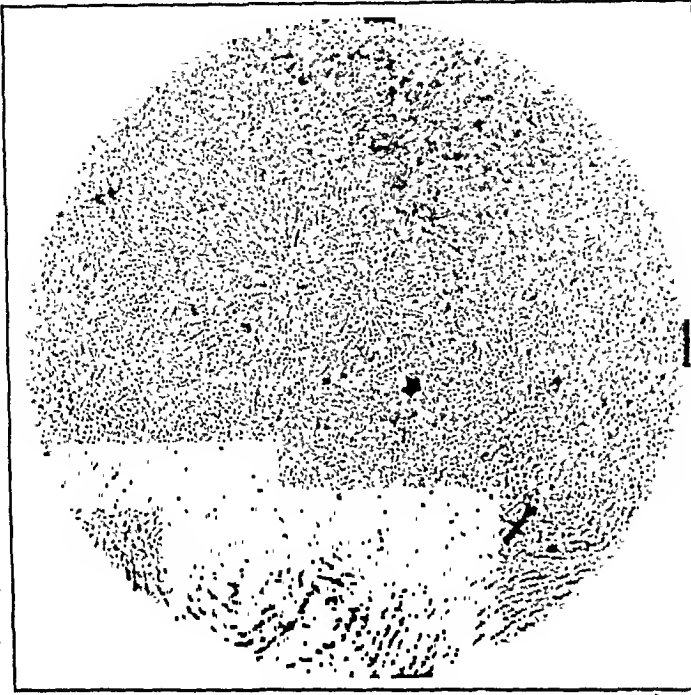


Fig. 3.—Rings and radiant formation. Pregnancy.

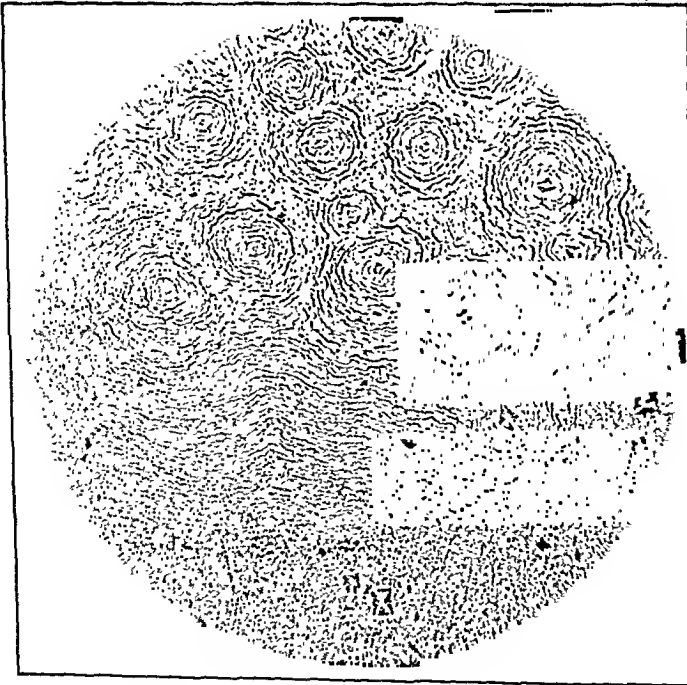


Fig. 4.—Rings and lines. Male serum.

As shown by the chart there is no distinct form correlated with any specific period of the endocrine status of the blood. Especially is there no clear indication of a definite form of crystallization in the different

III. Operations are unnecessary in: Cephalhematoma and engorged breasts.

IV. Both operation and treatment come later in: undescended testicle, harelip (cleft palate), hydrocele and inguinal hernia, pyloric spasm or stenosis, and exstrophy of the bladder.

V. Operations are practically useless in: Spina bifida and tracheo-esophageal fistula.

Taking up first imperforate anus. This anomaly occurred 27 times in 93,000 out-patient deliveries at the New York Lying-In Hospital, about once in 3,500 cases. It is supposed to be the result of an arrest in development of either the anus or the rectum at about the sixth or seventh week of embryonal life, and is associated not infrequently with various fistulas connecting with the bladder, urethra or vagina. Calculation of the value of surgical intervention depends upon the absence of other abnormalities of the alimentary canal, and the proximity of the rectal pouch to the perineal surface. Wagenstein and Rice¹ have proposed an x-ray diagnostic test which is of the greatest value in determining these points. If the child is held upside down in the inverted position by the lower extremities the gas in the rectum will rise to the top,

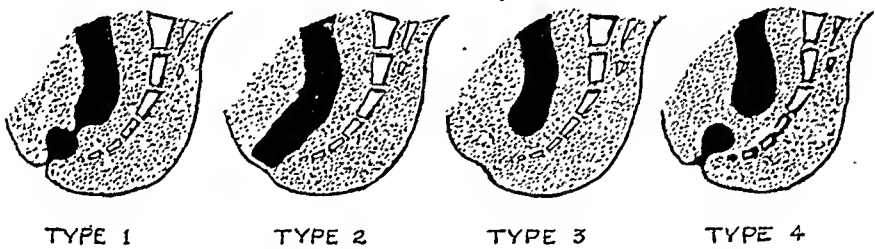


Fig. 1.—Four commonest types of anal atresia. (Adapted from Ladd and Gross.)

and the bubble will indicate the distance between the rectal culdesac and the skin of the anal dimple when a flat x-ray plate is made. The presence of this bubble will prove the absence of other intestinal deficiencies. The picture is best taken twenty-four hours after birth, by which time sufficient gas will have developed in the intestine.

Ladd and Gross² have recently shown that this anomaly occurs in four types.

Type I is an incomplete rupture of the anal membrane, or a stenosis 1 to 4 cm. above it. The symptoms are ribbonlike fecal movements accompanied with straining. The treatment is repeated dilatation. Their result in 21 cases of Type I was a mortality of 9.5 per cent.

Type II is a true imperforate anus. The obstruction is due to a persistence of the membrane at the anal orifice. The treatment is simple crucial incisions. Their result in 6 cases was a mortality of 16.1 per cent.

Type III is the most common variety of imperforate anus. The anus is absent but there is a descending rectal pouch approaching to within 1 to 4 cm. of the anal dimple. The treatment is a perineal incision with dissection upward, exposing the rectal pouch. This is then brought down and sutured to the margin of the skin incision. Their result in 117 cases was a mortality of 24.8 per cent.

I have operated upon two cases of this type. Both recovered and had good sphincteral control up to the age of two and four years when last observed. The

ditions which we studied. However, the dried drops of diluted blood serum from women do not show sufficiently clear pictures to be of any help in evaluating amounts of circulating hormones. It appears altogether doubtful if any form of crystallization of diluted blood serum expresses the endocrine status of the blood.

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44 EAST SEVENTY-EIGHTH STREET

40 EAST EIGHTY-EIGHTH STREET

WORTH-WHILE SURGERY IN THE NEWBORN*

JAMES A. HARRAR, M.D., NEW YORK, N. Y.

(From the Lying-In Hospital)

WHILE the two specialties are closely associated where neonatal care is concerned, nevertheless there is a gap between the domain of obstetrics and that of pediatrics where the responsibility for handling the surgical emergencies of the newborn is rather ignored by both. The obstetrician, being surgically trained, certainly is better equipped to fill this gap than is the medically trained pediatrician. The general surgeon may be called upon for help, but the obstetric specialist should be able from his experience to distinguish those conditions in which operation is profitable.

Certain children are born with developmental somatic abnormalities and others with birth trauma. Many of these conditions are, of course, incompatible with survival, and some, temporarily amenable to operative treatment, subsequently prove to be virtually hopeless. However, in certain deformities and injuries, promptly performed operation is imperative and life-saving, while in others treatment could be and should be initiated by the obstetrician during the neonatal period.

It is the purpose of this discussion to enumerate the more obvious abnormalities and injuries that may be properly subjected to surgical treatment, to briefly describe the procedures that have proved successful, and to urge upon the obstetrician the advantage of initiating the appropriate remedial measures himself.

We might summarize these conditions in the newborn as follows:

I. Operations are of value in: Imperforate anus, amniotic hernia and hernia into the cord, supernumerary digits, phimosis, and tongue-tie.

II. Early treatment is important in: Brachial birth palsy (Duchenne's) (Erb's), fracture of the long bones, depression of the skull, forcep-blade pressure marks, and deformity of talipes (clubfoot).

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I wish to report two personal cases of this type, true amniotic hernia. The first was a premature infant born at the hospital in 1923. There was a deficiency at the umbilicus, mostly above the insertion of the cord, 3 by 4 cm. in extent. The hernia protruded but a centimeter above the surface of the abdomen, and was covered with a translucent membrane through which intestinal coils could readily be seen. On account of its prematurity I feared that the child would not survive operative treatment. Sterile gauze dressings were, therefore, applied beneath a bandage support. The thin layer of amnion gradually dried and separated from the underlying peritoneum which simultaneously was covering with granulations as the abdominal wall contracted. Spontaneous recovery occurred and by the fourth week the baby had quite a satisfactory looking umbilicus with very little protrusion.

My second case was of the more extensive type already referred to. On Dec. 23, 1934, after a five-hour labor, a thirty-four-year-old primigravida delivered herself spontaneously of a 2,950 gm. male infant. There was some trouble in delivering the

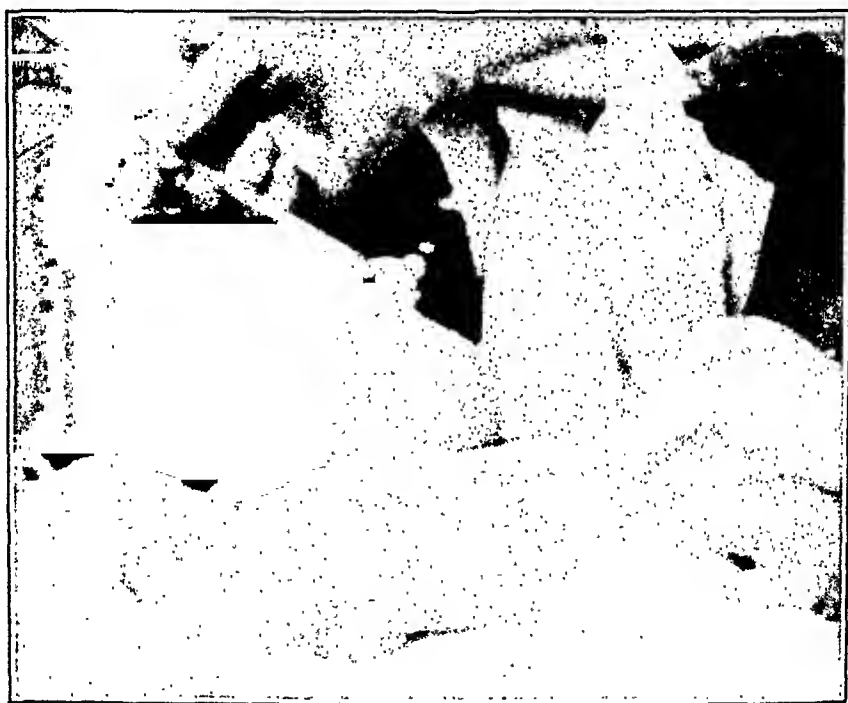


Fig. 2.—Author's second case of amniotic hernia. Sac containing entire liver and intestines. Before operation for radical cure.

trunk of the child caused by the presence of a large mass attached to the abdomen of the baby. This mass proved to be a large amniotic umbilical hernia 8 by 10 cm. in size. The sac was translucent and through its walls could be seen the entirely eviscerated liver and coils of intestines. The cord was attached to the summit of the sac, the vessels coursing down its lower half to enter the abdomen at its lower margin. The cord was tied and cut and the infant wrapped in a sterile towel. Six hours later under light ether anesthesia the contents of the sac, including the entire liver and gallbladder, small intestines, cecum and appendix, and part of the stomach, were reduced by taxis. The opening into the abdomen was slightly smaller than the greatest circumference of the sac, and some difficulty was experienced, especially with the liver. Finally after making firm squeezing pressure it was possible to reduce the size of the liver sufficiently to push it into the abdominal cavity, at which moment it slipped into place below the diaphragm. While pressure with gauze was maintained by the assistant, the sac was opened at its upper margin and gradually cut

sphincter muscle is always present and is not dependent upon development of the lower rectum. I have found the ordinary nasal speculum helpful in getting good exposure. The rectum, distended with meconium, is best found by carrying the blunt dissection close to the anterior surface of the sacrum. This also obviates injury to the urethra in the male.

Typo IV is really an imperforate rectum. The anal opening and lower rectal segment are normal. The descending segment of rectum, however, ends blindly, the obstruction being 2 to 4 cm. above the anus. In 18 cases of this type the mortality of Ladd and Gross was 61.6 per cent. It is the most serious of all, as an abdominal operation becomes necessary to effect a cure. We had one such case at the old Lying-In. It was easy to take the rectal temperature in the rectal pouch and the condition was unrecognized for several days. A colostomy was then done but the infant died on the fourth day of peritonitis. A similar case occurred in the new Clinic. A colostomy was done on the third day on the general surgical service; the infant died shortly after the operation.

Congenital anomalies at the umbilicus have been clinically divided by Cullen³ into three groups:

1. The small umbilical hernia or protrusion which is quite common and is best treated by adhesive strapping during the early weeks. I might add that the strapping should be a wide strip so applied as to conform to the curve of the abdomen and carried well up around the dorsal flanks. If kept dry it need be removed but once in five days.

2. Hernia into the umbilical cord. In the early weeks of fetal life the greater part of the small intestine lies within the umbilical cord. The intestine gradually withdraws into the abdomen and the cavity in the cord becomes obliterated. This may not occur and true hernia into the cord remains. The umbilical opening of such a hernia is relatively narrow, and this as well as the presence of adhesions frequently makes reduction impossible without first enlarging the opening. These adhesions were a source of difficulty in a case recently reported by Haines and McElroy.⁴

3. Amniotic hernia. This condition is also known as abdominal exstrophy, eventration, ectopia of the abdominal viscera, gastroschisis and massive umbilical hernia. There is an absence of the abdominal wall around the umbilicus, the defect being replaced by amnion reflected from the cord over the abdomen and lying directly upon the peritoneum. There are thus two layers to the thin translucent sac. If the abdominal walls are greatly lacking, a large hernial protrusion naturally tends to occur owing to intraabdominal pressure. The sac may contain the small and large intestines and even the liver. There are frequently light adhesions of the anterior surface of the liver to the sac wall.

The amniotic hernia does not interfere otherwise with the development of the fetus, but the only chance of the infant's survival, except in the deficiencies under 3 cm. in diameter, lies in an immediate operation for radical cure of the hernia. Von Reuss⁵ claims that in operations performed after six hours the mortality rapidly rises. A case or two of this type occurs in the literature every year. Where there is no accompanying abnormality, the mortality is invariably due to infection. Dr. Wing, of the Lying-In Staff, in 1922 successfully operated upon such a hernia containing the liver and intestines. He will more fully report the case and its progress to date in the discussion.

Injuries about the shoulder joint are the result of difficulty in delivery of the arms. They occur in vertex deliveries when the baby is large, and in breech deliveries when the arms are extended, and should receive prompt attention. Inability or disinclination to move the arm, or expression of pain on passive motion suggests one of three injuries: (1) Fracture of the clavicle; (2) laceration of the nerve roots of the brachial plexus, resulting in brachial birth palsy; (3) separation of the upper epiphysis of the humerus.

Fracture of the clavicle and separation of the upper epiphysis of the humerus occur oftenest in breech deliveries with extended arms. They are best avoided by using Potter's method of delivering the scapula

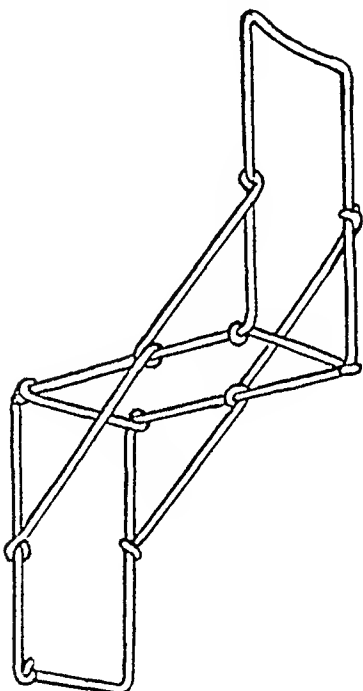


FIG. 3.



FIG. 4.

FIG. 3.—Wire splint for immediate fixation of the arm in brachial birth palsy. It is easily made of iron wire and of a size to fit the individual baby.

FIG. 4.—Showing placing of unpadded wire splint for brachial birth palsy. The baby's hand is incorrectly shown in pronation.

first before attempting to dislodge the arm. Brachial birth palsy is chiefly due to excessive traction on the head and lateral angulation of the neck in delivering the anterior shoulder in vertex presentations with a big baby. If moderate traction accompanied with fundal pressure will not suffice, the shoulder difficulty is best overcome by a deep episiotomy and insertion of the operator's half hand posteriorly to bring the posterior shoulder down first.

Immediate fixation is the proper treatment of all of these shoulder injuries, but especially in the birth palsy, known also as Duchenne's or Erb's paralysis. In this injury the arm lies motionless alongside the

away, placing through-and-through sutures of silkworm-gut as the incision proceeded. The anterior and upper surfaces of the liver were adherent to the inner surface of the sac, and blunt dissection left a moderately oozing area on the liver. The greatest tension in closing was in the upper third of the incision. As the lower angle was reached, the closing was carried on at an angle to the left, as there was more tissue there and less tension. The urachus was ligated and cut as it lay with the cord vessels close to the bladder. The baby stood the operation well, the breathing being a little fast and labored after closure, due to the abdominal tension. The baby had difficulty in retaining its feedings during the first few days and resort was had to clysis. The wound healed by first intention. By the tenth day the baby had developed a double inguinal hernia for which a truss was shortly applied. The child is now two years old, runs about and is progressing nicely. There is an area 8 cm. in diameter between the region of the umbilicus and the ensiform where the abdominal wall is weak, and protrudes on effort, somewhat resembling an incisional hernia. Later repair will improve this condition, but he has long ago been turned over to the surgeon for further rehabilitation.

In the newborn male, phimosis is to a certain extent a physiologic condition. Epithelial adhesions are always present between the glans and the mucous membrane, gradually loosening in the course of the first few months or years. In many cases forcible pushing back of the foreskin is all that is necessary. But a too long or too narrow preputial opening may require operative treatment.

Neonatal circumcision is a minor operation frequently referred to the assistant or the interne, who is sometimes disposed to make an unnecessarily bloody and elaborate operation out of it. The best result is obtained by following more or less the simple procedure of the ritual circumcision. An important point to avoid is trimming away any of the mucous membrane. Thus the frenal artery is avoided, and the sensory nerve endings at the frenum are preserved, if the initial incision is made as done by the Rabbi. To get this result the adhesions of the foreskin to the glans are first broken up with a probe. It is best not to do a preliminary retraction of the foreskin. A plain slotted circumcision guard is slipped on obliquely from above downward and forward, being careful to get the frenal raphe in the median line below. One snip of the scissors removes the excess skin beyond the guard, and a dorsal slit of the internal preputial membrane completes the operation. This dorsal slit is known as the "prea" by the ritual operators, and they lay great stress upon it. Careful retraction of the mucous membrane is then made and the dressing applied. Sutures and ligatures in this method are generally unnecessary, but three or four fine catgut sutures may be inserted if desired. The most effective dressing is a half-inch iodoform gauze strip twelve inches long applied as a little roller bandage and tied with a thread. This dressing is allowed to remain in place for three days. It controls any oozing, acts as a splint to the wound and prevents the usual edema at the frenum that results when merely the ordinary vaseline dressing is applied.

Forceps blade pressure marks in the superficial soft tissues, especially over the forehead, may be cosmetically improved by immediate subcutaneous injection of a small quantity of normal saline solution, followed by gentle massage.

The deformity of talipes, planus or valgus, can be treated from birth with daily massage and manipulation. If this is conscientiously done, in the milder cases, plaster splints and tenotomy may often be found unnecessary.

In 1916 at the old Lying-In, having operated with unsatisfactory results on several cases of spina bifida, I took the opportunity of reviewing the hospital cases up to that time.⁸ I found that in 91,600 confinements there had been 59 instances of spina bifida of all types, and nine others not confined by us had been referred to us for care. The following were my published results: 7 were stillborn; 30 were treated without operation, all dying within a few weeks; 31 were subjected to radical operation for the cure of the rachocoele.

An equally unfavorable prognosis followed all the operative cases, and it seemed very doubtful whether operation was of any real benefit to the infant, even if it was successful. Of the 31 operative cases 18 patients died within one to twenty-two days of meningitis, encephalitis, and general infection.

Thirteen recovered from the operation with solidly healed scars. Of these, 9 died later of increasing hydrocephalus and inanition. Of the remaining 4 healed operative cases, 2 were discharged with increasing hydrocephalus and spastically paralyzed legs, one at the time of my investigation was two and one-half years old, a helpless hydrocephalic idiot with spastic legs, and one was living and well at three years of age, having been operated upon at the fourth week for a simple meningocele. All authorities agree that simple meningocele in its pure form is very rare.

Although occasional cases of satisfactory surgical cure of spina bifida are on record, a recent review which I made of 13 cases occurring in the first 10,099 confinements at the new Lying-In (4 of which were operated upon by the neurologic surgeons on the General Surgical Service of the New York Hospital) gave me no encouragement to alter my opinion that, except in the simplest meningocele with no hydrocephalus and no paralysis, operation for the cure of spina bifida is rarely of permanent value.

Instances of the tragic anomaly, tracheo-esophageal fistula, though infrequent, are familiar to most of us. Plass⁹ who, in 1918 found 136 actual cases in the literature, states that the condition was first described in 1696 by Thomas Gibson. At the New York Lying-In Hospital the incidence was about 1 in 7,000, five recognized cases occurring in the last 36,000 confinements. In this condition the descending segment of the esophagus ends in a simple culdesac, while the ascending segment almost invariably opens into the trachea at about its bifurcation. The child is often an otherwise full-grown healthy infant. The prompt regurgitation of all fluids swallowed, followed by attacks of cyanosis, first calls our attention to the state of affairs. Another suggestive symptom is the constant driveling of mucus and saliva from the mouth. It is impossible to pass a catheter more than 12 cm. from the alveolar

body and is rotated inward. There is no swelling or unusual mobility about the shoulder joint and x-ray is negative. Binding the arm to the side is useless and even harmful. It is important to keep the arm abducted to 90 degrees from the beginning. I wish to present a simple wire splint for use in the brachial plexus injury. This can easily and quickly be made from a bit of iron wire with a pair of pliers. Bound with tape, then properly padded, it may be applied at once after birth. This holds the arm in the commuter's strap hanger position, shoulder joint and elbow both at right angles and the hand supinated. The sooner the arm is placed and maintained in this elevated position, the less the hemorrhage and laceration of nerve tissue, and the sooner the process of repair can begin.

This simple bit of apparatus most effectively tides over the time until the orthopedic surgeon can take the case in charge. I have seen several cases of the milder upper arm type of brachial birth palsy completely recover after wearing such a splint for a few weeks.

In fracture of the clavicle, crepitus can usually be elicited and x-ray evidence is conclusive.

In the rarer accident of separation of the upper epiphysis of the humerus, known also as birth dislocation of the cartilaginous epiphysis, there is abnormal mobility between the shaft of the humerus and the upper epiphysis, though bony crepitus is difficult to obtain. By the second day a large firm swelling, often evidently tender, has developed along the upper third of the humerus. Immediate x-ray is likely to be indefinite. Truesdell⁶ was the first to demonstrate that an x-ray, taken on the tenth to twelfth day, will demonstrate the presence of new bone about the upper portion of the humeral shaft. This has been deposited beneath the periosteum stripped up from the shaft of the bone as a part of the lesion of epiphyseal separation, and produces the characteristic x-ray appearance of this birth injury.

Fractures of the long bones during delivery occur near the middle of the shaft. An injury near the end of a long bone in an infant usually proves to be a separation of the epiphysis rather than a fracture. Union of fractured bones in the newborn is so rapid that on the basis of weeks as suitable in the treatment of fractures of adults, we must reckon with days in infants. Soft callus appears even in a few days and bony callus has been observed even in the first week.⁷ Treatment consists essentially in fixation and traction in an attitude that best maintains the fragments in position.

Depression of the skull from promontory pressure should be buckled gently into place by elevation of the bone with one blade of a single tenaculum forceps. The bone is most easily raised immediately after birth.

One condition which Dr. Harrar did not mention is atresia of the small intestines. While it is usually true that these atresias are multiple and in consequence not amenable to surgery, yet occasionally one does encounter single obstructions, oftentimes in the jejunum, which, if promptly operated upon, can be life-saving. I can recall at least two such instances, where the symptoms of high intestinal obstruction became evident during the first hours of the baby's life and a prompt operation served to correct the condition.

In all probability circumcision is usually not necessary. The reasons for its being done are partly cosmetic and partly the fact that it makes the toilet of the child's genitalia a little easier. The strongest indication for doing circumcisions is that people want their babies circumcised, and since it is a simple operation without harmful effect it should be done if the condition of the baby warrants it.

The prompt treatment of depressed fractures is an important question. The small depressions of a baby's rather soft and elastic skull can be corrected within the first few days of life. If it is not done promptly, there is soon enough formation of new bone to render it quite impossible to spring the depression back into place. Then the only procedure possible is the removal of the whole depression, leaving a deficiency in the skull at that place. Most of these babies who have depressed fractures which are uncorrected suffer no ill effects from them, but occasionally, later on, one does see convulsive seizures which presumably have their origin in fractures which occur during birth.

In my experience the simpler forms of clubfoot which can be corrected by massage and early bandaging are not as common as the ones due to bony deformities and which require rather prolonged and vigorous orthopedic treatment. If the deformity is at all severe, the patient had better be put rather early under the care of a competent orthopedic surgeon. It is undoubtedly true that the earlier treatment is instituted, the earlier cure is effected.

It is theoretically possible to effect a cure of a simple meningocele, but, as Dr. Harrar has said, simple meningoceles are very uncommon. In true meningo-myelocele, even though the spina bifida can be corrected cosmetically, extensive paralysis remains and chronic hydrocephalus usually results. There are cases in which the hydrocephalus becomes arrested without serious brain damage but even in these instances we have an individual with paralyzed lower extremities and lack of sphincter control, who can never be a thoroughly adequate human being.

DR. LUCIUS A. WING.—This patient, whom I am presenting, now a boy in his fifteenth year is the case with the large hernia into the amniotic sac to which Dr. Harrar referred.

This boy was a first child and was born Dec. 26, 1922, in the Outdoor Department of the Lying-In Hospital. He was brought to the hospital immediately after birth, probably with some contamination of his abdominal contents. He was taken to the operating room and warm saline was copiously flooded over the prolapsed bowel and exposed liver. Under ether, the amniotic sac was cut away from its peritoneal attachment, the intestine was replaced, and the liver, which it did not at first seem possible to get into the abdomen, was reduced somewhat in size by pressure until most of the blood was squeezed out of it and then pushed back into the abdomen. The normal conformation of the diaphragm was absent. There was considerable difficulty in closing part of the abdominal defect. The lower part was brought together without much tension, but the upper part was simply latticed across with silkworm-gut. The granulations and extensions of epithelium from the edges of the wound were rapid and at the end of three weeks there was a combination of epithelial and granulation tissue covering.

By the time he was four and one-half months old he had overcome all his early feeding defects, and weighed 16 pounds. The boy went to school at the usual time

margin, and x-ray confirms our diagnosis. Operative treatment up to date is of no avail. The first thought is gastrostomy in order to provide nourishment to the hungry infant. But any fluid placed in the stomach through such an opening is almost immediately coughed up through the nose and mouth as I learned from my experience in performing such a gastrostomy on a case in 1919. Similar results of the failure of gastrostomy were reported by Mathieu and Goldsmith¹¹ in 1933, and the inadequacy of gastrostomy was again proved in a case occurring in the clinic recently and operated upon on general surgery, the infant promptly dying of pneumonia from regurgitation of stomach contents into the lungs. Wing and Losee, after study on a cadaver in 1920 at the Lying-In Hospital, did an exploratory thoracotomy from the dorsal approach on a living infant but without success; finally in 1923 they succeeded in making a transthoracic esophageal anastomosis, but the shock of the procedure was again too much for the infant.

The surgical handling of this anomaly, if it is ever perfected, will be beyond the equipment and skill of the obstetrician. It is evident that a "restitutio ad integrum" of the esophagus does not yet seem feasible, and that without this, life, even if possible, would be intolerable, and it were better to let the baby alone.¹²

CONCLUSIONS

1. I see no reason why the modern obstetrician with hospital facilities, and trained as he is in gynecologic surgery, cannot undertake operations for the cure of imperforate anus and umbilical hernia in the newborn.

2. He should pay more attention to the technique with which his neonatal circumcisions are done.

3. He should be prepared to diagnose and initiate treatment in the brachial birth palsies, fractures, and the milder deformities.

4. Operations for the cure of spina bifida and especially tracheo-esophageal fistula are as yet beyond the field of the obstetrician, and the family should be fully informed of the poor outlook for any surgical intervention.

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DISCUSSION

DR. OSCAR M. SCHLOSS.—The baby, certainly during the early stages of his life, is not merely a by-product of the obstetrician's efforts, but really is his patient. Upon him devolves not only the duty of insuring appropriate treatment of such diseases or anomalies which can be appropriately treated, but also of recognizing them promptly.

foreskin is very tight and very long, I advise circumcision. In these very tight foreskins there is great possibility that retraction will cause edema, splitting, bleeding, and swelling, and I prefer circumcision.

Where there is one deformity, one may expect to find two or three deformities, and it, therefore, is infrequent that we get a suitable case for operative work in most of the alimentary abnormalities. The holding of the baby upside down to get the gas bubble picture in imperforate anus is a valuable aid, and it shows also that no other abnormality or deformity is present. I think it is well worth while.

Pylorospasm is rarely a neonatal condition. It begins usually after the first few weeks. We see quite a few cases of the milder type of clubfoot. I am sure they are frequently cured by manipulation before the pediatrician sees the baby, clearing up in the first ten days or two weeks.

OBSTETRIC ANALGESIA WITH ACID ALURATE IN RECTAL ETHER OIL

HAROLD C. INGRAHAM, M.D., AND JAMES ALAN ROSEN, M.D.,
NEW YORK, N. Y.

(From the Department of Obstetrics, Lincoln Hospital)

GOULD and Hirst have recently completed a survey of the leading obstetric clinics in this country and the diversity of methods and results show that the ideal drug or combination of drugs for the alleviation of labor pains has not as yet been found. Ideally analgesia should comfort the mother, should not prolong or disturb labor, or tend to postpartum atony and hemorrhage in the mother, and should not produce unfavorable results in the baby.

Many techniques have been elaborated both here and abroad which include the barbiturates as a base, but none of these are without disadvantages when compared with the ideal criteria cited. In the method here reported a combination of drugs was sought which not only fulfilled the criteria but which could also be given under all conditions with simplicity and ease and result in a period of analgesia and amnesia. Comparative studies of the barbiturates by Nielson, Higgins, and Spruth have shown that alurate (Hoffman-La Roche) has a relatively high margin of safety as well as a prolonged action. Tritsch and Brown in their study of barbiturates in labor, found the sodium salt of alurate to be more efficient than any other barbiturate which they tried. However, alurate, like most of the other barbiturates has a tendency to excite women in labor and various methods have been used to offset this disadvantage, among which the rectal installation of ether oil has been most popular. Acid alurate or allyl-isopropyl barbituric acid is completely soluble in alcohol and ether and therefore in the rectal ether oil mixture devised by Gwathmey. Since a combination of drugs which could be given at one time would be advantageous and inasmuch as rectal ad-

and did well, although his ability to take large meals was not quite that of a normal youngster. When he was nine years old an x-ray gastrointestinal series was made. After the age of ten he apparently turned the corner, and now he eats everything and apparently has no gastrointestinal symptoms whatsoever.

The embryology of this condition is of interest. Until the end of the tenth week, the midgut is entirely in the special amniotic sac, and rotation of the small intestine takes place in this sac. At the end of the tenth week, retraction bands from the mesentery draw the intestine into the abdominal cavity. In these large protrusions into the amniotic sac, apparently this rotation does not take place. In this case the mesentery did not assume or take its normal attachment. Instead of running from left to right, the x-ray evidence obtained from the cycle taken at the ninth year is that the mesentery runs in the opposite direction. In addition, the large intestine, and cecum, did not descend or rotate in the normal manner.

The main danger in regard to the surgical conditions of the newborn is that the obstetrician may overlook the simpler types of injuries. Even the fractures are not always evident, and if a casual examination is made they may be overlooked. In November, 1936, Thorndyke and Pierce reported from the Surgical Service at the Children's Hospital in Boston, something over a hundred cases of fractures in the newborn. One-third of them were unrecognized at the time of their occurrence.

DR. ARTHUR W. BINGHAM.—About twenty years ago I ran across three patients with spina bifida who were operated upon and all three remained under my observation to the age of twelve years. They, of course, were not severe cases, and none of them had paralysis. I did not realize that the first one could be operated upon and told the family it was useless to attempt anything. However, the surgeon thought he could improve the condition and he got a very good result. In the next two years I had two more cases and the same surgeon operated upon them successfully.

DR. E. EVERETT BUNZEL.—In cases, such as Dr. Wing's we are perfectly justified in attempting the type of surgery which has been demonstrated by him. The only alternative is death by peritonitis. I saw a case, however, where complete evisceration of the liver, intestines, kidneys, and bladder presented themselves to us at birth, and in which the placenta was attached to the liver. Obviously, there was not very much that could be done in such an instance.

The question of circumcision has been brought up rather more fully tonight than I ever heard it discussed. Routine circumcision is condemned by many pediatricians because of fear that it will produce irritations and lead to certain bad habits which circumcision is claimed to obviate. It is still a question in my mind whether we should advocate it always, or advise it only when congenital phimosis exists.

The differential diagnosis between pylorospasm and pyloric stenosis may be difficult. I have observed a case in which a mass was felt in the upper abdomen, but in which it was thought advisable to wait twenty-four hours before operating. In this interval the mass disappeared. The child (a male), who had developed symptoms on the eighth day, also had less vomiting in the next twenty-four hours.

The diagnosis was changed from pyloric stenosis to pylorospasm. He was then treated with atropine and clyses and given as much fluid by mouth as he could stand. The child survived without operation.

With clubfoot, we are again dealing with a condition where mature judgment is essential. With the advice of an orthopedist, by manipulation and massage, by strapping, and splinting, we may obviate operation.

DR. HARRAR (closing).—The question of circumcision is always a difficult one. The family ask you if it should be done and you do not know whether to say it should or should not be, nor is the pediatrician usually so sure about it. If the

TABLE I. GENERAL SUMMARY

	PRIMIPARAS PER CENT	MULTIPARAS PER CENT
Analgesia		
None	2	0.0
Moderate	15	15.0
Good	83	85.0
Amnesia		
None	21	34.0
Fair	35	17.5
Complete	44	48.5
Apnea of babies	14	12.5

TABLE II. RESULTS WITH RELATION TO LENGTH OF LABOR

	AVERAGE LENGTH OF LABOR PER CENT	AVERAGE LENGTH OF LABOR AFTER INSTILLATION PER CENT	DURATION OF EFFECT PER CENT
4 hours or less	2	46	2.0
4-12 hours	36	40	88.0
12-20 hours	22	14	9.3
20-24 hours	24	0	0.0
More than 24 hours	16	0	0.7

In going over our charts carefully, we feel that although we did no hysterographic studies of uterine contractions, in only 5.6 per cent of all our cases were the forces of labor decreased, while in 63.5 per cent labor appeared to be increased in intensity. In all our cases of delayed labor no ill consequence resulted, and we feel that possibly in these cases, too much stress was placed on subjective complaints and the medication given too early. In one case of primary inertia, labor was stimulated following the medication.

At first, nontoxic cases were selected without prejudice, but rapidly all types of cases were included in the series such as toxemias, cardiacs, and tuberculous patients.

The method of delivery is of some interest. We used prophylactic low forceps quite frequently. In no case were forceps used because of too great a decrease in the expulsive forces, making for long second stages if intervention were not practiced. In fact, all our forceps cases except those done because of fetal indications would probably have delivered normally.

TABLE III. METHOD OF DELIVERY

	PRIMIPARAS	MULTIPARAS
Normal	47	30
Low forceps	70	10
Midforceps	9	0
Breech extraction	7	0
Version and breech extraction	2	0

Supplementary anesthesia was given in 60 per cent of the cases, mainly those in whom operative interference was used. Of these 25 per cent were delivered instrumentally, using only 1 per cent novocaine in the form of perineal infiltration, with very marked success. In one case analgesia was so good that a low forceps delivery was effected without supplementary anesthesia. All of these subsequent anesthetics were given by interns, and in practically every case induction was easy, little anesthetic was needed, and there was a complete absence of respiratory complications.

ministration obviates the possibility of gastric irritation and does away with the discomfort of hypodermic injection, it was felt that the method here reported was worthy of clinical trial. The results are based on a study of 175 cases, 135 primiparas and 40 multiparas in whom a definite routine as given below was followed.

TECHNIQUE

Subjective complaints of pain are taken as the indication for the administration of the analgesia and in primiparas this usually occurs when the pains are regular and strong, coming on every seven to five minutes, lasting from twenty to thirty seconds. In multiparas, similar criteria are used although these are not always so characteristic. The cervix is usually from 2 to 2½ fingers dilated, but more attention is given to the character of the pains rather than to the condition of the cervix. The mixture used in this series consists of 2½ ounces of ether, 20 gr. of quinine, 1 drachm of alcohol and 12 gr. of alurate, in crystal form, with enough olive oil to make 4 ounces. This is given as a retention enema, the rectum previously cleansed by the usual soapsuds enema. Usually thirty minutes or more is allowed to elapse from the time of the enema to the instillation of the analgesic solution. Most of the patients retain the enema well and in our series there were no complaints of incidental proctitis. In 94 per cent of the cases there was noticeable effect on the patient within thirty minutes, while in 6 per cent it took forty-five minutes or longer before effects were noted. The standards used in evaluating our results are as follows:

1. Analgesia was necessarily objective and *good* analgesia implied little or no response to uterine contractions. *Fair* analgesia involved changing positions and outcries but less than would be expected without drugs, and *poor* analgesia meant little or no response to drug administration.

2. Amnesia was determined by test questions of enumeration of events from time of administration of the drug to the time of delivery or awakening. Thus, complete amnesia evinced absolutely no recollection of events, and moderate amnesia implied incomplete or hazy recollection of events.

3. Excitement was judged by the degree of physical activity of the patient as well as her noisiness. This is also involved in our evaluation of analgesia. Excitement was noted only for those cases where muscular restlessness was so marked as to require restraint.

4. Apnea of the infant means that the child was born not breathing and required some resuscitative measures, though in our series, only the use of the pharyngeal Flagg apparatus was needed.

REPORT OF CASES

Detailed records were kept on each patient, and from these the final analysis was made and graded.

From Table I it can be seen that the results were worth while in most of our cases. Furthermore, in not a single case did we observe any excessive postpartum hemorrhage or atony of the uterus.

One important factor in judging any form of analgesia during labor is the effect which it has on the uterine contraction and the progress of labor. Obviously, any medication which delays or stops the process of delivery has to be amended or discarded. Our observations lead us to believe that labor is hereby enhanced as may be seen from Table II.

CLINICAL EXPERIENCE WITH A NEW ERGOT ALKALOID*

JOHN E. TRITSCH, M.D., F.A.C.S., AND KARL H. BEHM, M.D.,
NEW YORK, N. Y.

(From the Department of Obstetrics and Gynecology, Metropolitan Hospital)

DESPITE the fact that ergot has been used clinically for more than a century, only in recent years have its specific alkaloids been isolated and applied therapeutically.

As early as 1875 Tanret¹ obtained a crystalline ergotinine from ergot but this alkaloid was only slightly active and possessed little or no pharmacologic or therapeutic significance. In 1906 Barger and Carr² discovered ergotoxine in amorphous form almost simultaneously with Kraft.³ Ergotoxine has recently been crystallized, and according to Stoll⁴ is isomeric with ergotinine. In 1920 Stoll⁴ isolated two new isomeric alkaloids, ergotamine and ergotamine, from ergot and in 1925 Stoeckel⁵ at the Gynecological Congress in Vienna called attention to the regular and constant effect of ergotamine as a uterine styptic.

In 1935 there appeared within a short period reports from four different investigators concerning a new ergot alkaloid, to which the Council on Pharmacy and Chemistry has since assigned the name ergonovine. Dudley and Moir⁶ called this new principle ergometrine; Kharasch⁷ and his coworkers ergotocin; Thompson⁸ named it ergostetrine and Stoll and Burekhardt⁹ ergobasine; a clear chemical definition was apparently first supplied by the two latter authors. Ergobasine is a typical ergot alkaloid of greater solubility in water than ergotamine but of lighter molecular weight. It acts more rapidly than ergotamine but for only about one-half as long according to Rothlin,¹⁰ who also says that while it produces a typical effect upon the uterus, it lacks completely the sympathicolytic property so characteristic of ergotamine and that its precise therapeutic value still needs to be clarified.

In an attempt to determine the action of the tartrate of ergobasine (basergin) clinically, we have used this drug in a series of 115 parturients of whom 36 were primiparas and 79 were multiparas. In order to obtain a more accurate appraisal of its action, we administered the contents of a 1 c.c. ampule of ergobasine, equivalent to 0.2 mg. ergobasine tartrate, intravenously immediately following the delivery of the infant so we could observe:

1. Time of recurrence of uterine contractions.
2. Time elap-ing from the end of the second stage to the delivery of the placenta.
3. The amount of bleeding following its administration.

After this, for the first two days of the puerperium we also gave our patients in this series one tablet (1 mg.) of ergotamine tartrate every four hours, and observed the height of the fundus above the pubis on

*Read before the Medical Staff of the Metropolitan Hospital, January 18, 1937.

There were three stillborn infants in the series: an anencephalic monstrosity and two macerated fetuses born from syphilitic mothers who had received inadequate antisyphilitic treatment. Asphyxia was seen in only 13 per cent, and all of these responded quickly and without difficulty to Flagg method resuscitation. No neonatal deaths resulted.

In every case the patients recovered completely from the effects of the medication though they usually slept soundly from four to seven hours after delivery and in some cases were even drowsy for a day. This we felt to be worth while since it gave the patient a good rest after her labor. The drug is apparently not of high grade toxicity because in one case, by accident, a patient was given a double dose, 24 gr., 2 instillations within fifteen-minute period. The only resultant complication following a short labor with delivery of a normal baby was that the mother slept too soundly for thirty-six hours. In seven cases dosage was repeated in the course of prolonged labors after periods ranging from eight to fourteen hours.

COMMENT

We are not convinced that the alurate technique as used is ideal, but it does deserve a place among the best procedures thus far. In the entire series there was not a single case that could be considered a complete failure. By failure we mean cases where there was neither analgesia nor amnesia. As regards excitement we found in our series that this great drawback to the use of the barbiturates was at a minimum. In only three cases, was there excitement enough to warrant restraint and in these cases though the excitement was almost maniacal the amnesia was complete. Although our method minimizes excitement it is still a method useful only in institutions.

CONCLUSIONS

1. In this series 99.3 per cent of the patients were benefited and 84 per cent could be considered successful as regards analgesia or amnesia or both.
2. The drug combination used here produced no serious or permanent effects on either the mother or child.
3. The length of labor tends to be shorter.
4. Apnea of the infants may be regarded as relatively unimportant both as to frequency and seriousness to the infant's life or health.
5. Constant and intelligent observation of the patient during labor is still necessary even with the low incidence of excitement, and the method should be limited to hospital use.

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ing blood loss, we have attempted to classify bleeding as "very slight," "slight," "moderate" and "profuse," it being assumed that "moderate" would correspond to average bleeding. Table I indicates the results from this standpoint.

TABLE I. BLOOD LOSS

	PRIMIPARAS	MULTIPARAS
Very slight	11	30
Slight	17	34
Moderate	7	13
Profuse	1	2

In the three cases in which bleeding was regarded as profuse, an additional ampule of basergin caused cessation of excessive bleeding. It is evident from the above tabulation that the majority of cases (92) had definitely less than average bleeding after the delivery of the infant and placenta.

THE PUERPERIUM

Ergotamine tartrate (1 mg.) tablets were given by mouth one every four hours for the first two days postpartum, and we here present charts indicating the average height of the fundus above the pubis on the day of delivery, first, second, third, fifth, and seventh days postpartum.

TABLE II. HEIGHT OF FUNDUS

DAY OF DELIVERY	PRIMIPARAS	MULTIPARAS
DD	11.8 cm.	13.9 cm.
1	12.7 cm.	12.5 cm.
2	10.85 cm.	11.2 cm.
3	9.6 cm.	10.0 cm.
5	8.8 cm.	8.8 cm.
7	7.0 cm.	7.5 cm.

The morbidity according to the B. M. A. Standard, is indicated in Table III.

TABLE III. MORBIDITY

PRIMIPARAS		MULTIPARAS	
Total fevers	5	Total fevers	3
Eliminate			
Respiratory	1		
Pyelitis	1		
Pulmonary tuberculosis	1	3	
Net morbidity	2 (5.5%)	Net morbidity	3 (3.8%)

The duration of labor averaged 13.7 hours in primiparas and 5.6 hours in multiparas.

The methods of delivery were as shown in Table IV.

different days postpartum as well as the incidence of postpartum fever. Finally, for the sake of completeness, we shall give some consideration to the types of delivery and duration of labor.

It is evident from published observations (see bibliography) that the average period of time elapsing from the delivery of infant to the time of the first uterine contraction when no medication is given is from five to twenty minutes, and the expulsion of the placenta occurs shortly thereafter; also that the administration of pituitary extract at the beginning of the third stage shortens this period to from five to eight minutes. In commenting favorably upon the small amount of blood lost when pituitary extract is given to shorten the third stage, Brodhead and Langrock, however, say, "The only drawback to the method in our small series of 100 cases, is the possibility of irregular or hour-glass contraction of the uterus which occurred in one of our series and which has occurred to the authors in several cases outside of this series where pituitrin was given. We recognize the fact, however, that this complication occurs independently of the use of pituitrin, and time only will prove and further investigation will be necessary to show whether this complication is directly attributable to the method or not.

"We believe that earlier removal of the placenta would probably have reduced the blood loss in some of our cases."

Let us now give consideration to the time elapsing from the administration of basergin to the first contraction of the uterus. In primiparas, the average time was thirty-four seconds and in multiparas twenty-two seconds. With one exception, the extremes were from practically spontaneous contraction to sixty seconds. In the exceptional case (a multipara), contraction of the uterus did not occur to a demonstrable degree.

The average duration of time from the delivery of the infant to the delivery of the placenta in primiparas was 2.93 minutes and in multiparas 2.96 minutes. In primiparas the extremes were from thirty seconds to twelve minutes. One case required manual extraction of the placenta due to contraction of the lower uterine segment and cervix, and is not considered in averaging the duration of the third stage. In multiparas the extremes were from fifteen seconds to fourteen minutes. In three cases of the latter some difficulty was encountered in expression of the placenta, separation having obviously occurred, but obstruction prevented the expulsion. However, no radical procedure was necessary to accomplish delivery.

Bleeding was, of course, an important factor for consideration. The observation of this factor was made by one of us in all the cases here presented and due to the inaccuracies of any known method of measur-

TESTICULAR TUBULAR ADENOMA (PICK)*

JAMES RAGLAN MILLER, M.D., HARTFORD, CONN.

AMONG the fascinating groups of tumors of the ovary which have been the subject of illuminating research in the past few years, none are of more interest than the arrhenoblastomas. All degrees of variation are found in this group. At one end are the immature tumors which can be differentiated from the immature granulosa cell tumors only by their masculinizing effect on the patient. At the other end of the group are the highly differentiated testicular adenomas, first described by Pick.⁶ These seldom produce masculinizing effects. An example of this latter group is presented:

Mrs. R. C. (Hartford Hospital, No. 299843), aged thirty years, married four years, no pregnancies, chief complaint sterility, first seen Feb. 1, 1935. Previous ap-



Fig. 1.—Fibroma of ovary showing corpus luteum and testicular tubular adenoma.

pendicectomy, 1922. Cystoscopy six years previously for kidney tract pain showed double ureter on the left. Recent pelvic examination disclosed a tumor, and operation was advised. The periods began at thirteen, were always regular every twenty-eight days, lasting two to three days, never excessive. Last previous period, Jan. 15, 1935.

Physical examination showed a well-nourished, medium-sized woman, with well-healed appendicectomy scar. External genitalia were entirely normal. There was slight chronic trachelitis with eversion, and the uterus was thought to be in movable retroflexion, with a tumor about 6 cm. in diameter which was thought to lie in the left posterior fundal wall. A myomectomy was advised with suspension of the uterus.

*Presented at a meeting of the New York Obstetrical Society, March 9, 1937.

TABLE IV. METHOD OF DELIVERY

PRIMIPARAS		MULTIPARAS	
Spontaneous	10 cases	Spontaneous	69 cases
Low forceps	26 cases	Low forceps	7 cases
		Breech extractions	2 cases
		Manual rotation of occiput posterior	1 case

CONCLUSIONS

1. Basergin is a powerful oxytocic, and when given intravenously at the beginning of the third stage, it caused uterine contractions to be resumed in an average period of twenty-two seconds and thirty-four seconds in primiparas and multiparas, respectively, in our series of cases.

2. This new ergot alkaloid shortens the third stage of labor to an average of 2.95 minutes.

3. Bleeding is definitely lessened, the majority (80 per cent) showing less than average bleeding.

4. In four cases hour glass contraction of unknown origin was met with in placental delivery, one of which required manual extraction.

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Pulvertaft, R. J. V.: Post-Hysterectomy and Puerperal Tetanus, Brit. M. J. 1: 441, 1937.

The author reports a fatal case of tetanus following a hysterectomy. Examination of the perineal dressings used before the operation revealed that they contained the tetanus spores and other anaerobic spore-bearing pathogenic organisms.

From the laboratory investigations, it appears that cellulose wadding, commonly used in perineal pads, is peculiarly apt to harbor anaerobic spores. The reason why cottonwool, which also consists of cellulose, is safer is not obvious. Cellulose is useful in industry, but when used unsterilized in medicine, it is dangerous. This source of contamination of the puerpera must be rigidly guarded against.

membrane. The supporting interstitial cells were irregularly oval in shape with oval round nuclei, and scattered through this tissue were larger, irregularly polygonal shaped cells, having a relatively clear cytoplasm and a rather small nucleus with a nucleolus present. Mitotic figures were extremely rare, so that the tumor cytologically did not appear malignant. The adjacent fibromatous tissue was not cellular and showed nothing remarkable. Numerous fat deposits were seen in the interstitial cells, when frozen sections were stained with Sudan III.

Microscopic sections were submitted to J. V. Meigs and F. B. Mallory of Boston, James Ewing, S. H. Geist, H. F. Traut and L. Motyloff of New York, Robert Meyer of Berlin, and Walter Schiller of Vienna. Sections are in the possession of the ovarian tumor registry conducted by New York Gynecologic pathologists. Various opinions were obtained, and differed in some minor respects, but the tumor was identified as one similar to that described by Pick in 1905.



FIG. 4.—High power like Fig. 3.



FIG. 5.—High power like Fig. 3.

Professor Meyer's report is as follows: "In the fibroma one sees several remnants of ovarian tissue, and in the fibroma part, unripe testis, as in the fetus, with many interstitial cells. It is a tumor hitherto not known of this precise nature." . . . "I cannot see that the testicular tissue takes part in the tumor formation, but rather the testicular tissue is undergoing an atrophic death in the fibrous tissue."

The tumor presents very well-preserved testicular tubules in a normal female without signs of masculinization. The tubules in this instance appear to be more perfectly preserved or developed than in the other cases in the literature, and considering the well-preserved interstitial cells, we are again reminded of the statement of Robert Meyer, speaking of arrhenoblastomas: "These are a group of tumors related from their morphological similarities which more often, and to a greater degree, cause masculinization the more the tumor differs from the testicle, i.e., the more unripe it is. This appears contradictory but it is a fact."

Operation, Feb. 2, 1935. Uterus was found anteflexed, and the mass proved to be a solid tumor of the left ovary. Two or three small, dark blood spots in the right ovary suggested endometriosis, but no implantations could be seen. The left tube and ovary were removed.

Clinically, this patient made an uneventful recovery. She was seen for follow-up examination on March 13, 1935, by the author, on Aug. 14, 1935, by Dr. W. F. Shallenberger of Atlanta, Georgia, and in October, 1936, by Dr. Barney Brooks of Vanderbilt University, Nashville, Tennessee. None of the three examiners observed any signs of abnormal development of the clitoris, hair arrangement, or other masculinization signs. Dr. Brooks reports relatively severe pain about six hours before the onset of menstruation. He removed a small, nonmalignant adenofibroma from the left breast.

Pathologic Report (Dr. W. Kendall. No. 35959): Testicular tubular adenoma of ovary (Pick). Macroscopic examination: Roughly trilobate mass 7 by 7 by 5

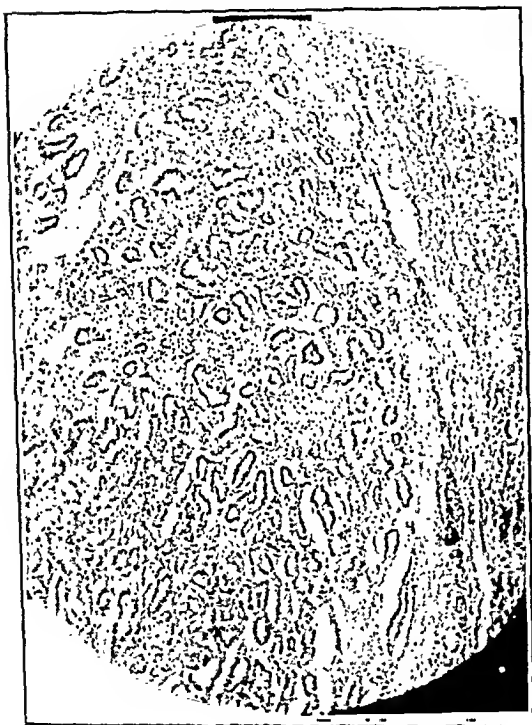


Fig. 2.

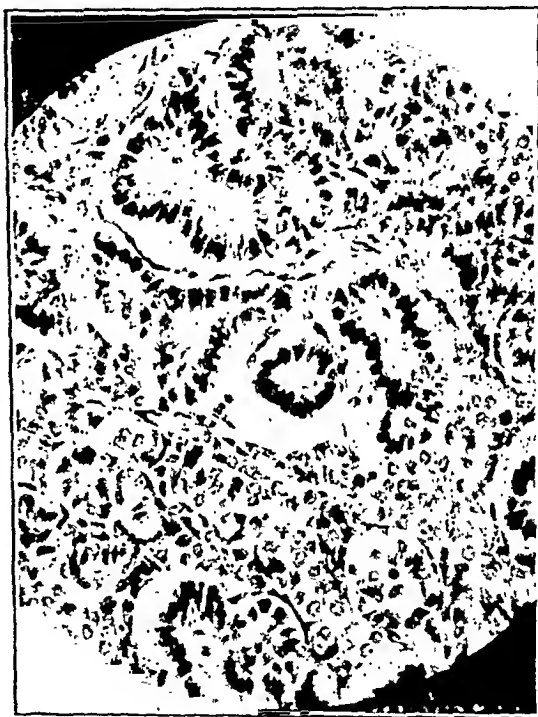


Fig. 3.

Fig. 2.—Low power showing tubular arrangement with many interstitial cells.

Fig. 3.—High power showing considerable shrinkage (paraffin) radially placed nuclei, columnar gland cells and interstitial cells.

cm. The greater part of the surface was encapsulated. On the capsule were seen numerous scattered bright red granular areas from pinpoint to 5 by 3 mm. in size. There was one cyst 5 mm. in diameter filled with dark blood. On section one pole was apparently normal ovarian tissue in which there were several follicular cysts 4 mm. in diameter, a corpus luteum 1.5 cm. and a peculiar lobulated, rather poorly circumscribed nodule 2 cm. in diameter, the cut surface of which had a yellowish brown color with a central zone of increased fibrosis. The remainder was a typical fibromatous tissue with glistening interlacing strands. Microscopic examination: Sections of the nodule described in the gross showed many small tubules lined by low columnar cells that had a slightly eosinophilic cytoplasm and an oval nucleus uniformly and rather deeply stained, and characteristically radially oriented. There was a moderate shrinking so that this layer of cells was separated from the basement

DISCUSSION

DR. SAMUEL H. GEIST.—I had the privilege of examining the tumor which has been reported this evening by Dr. Miller. It may very well be considered to represent an adenoma of the testicular part of an ovotestis, both because of its histologic appearance and because of the fact that a congenital abnormality of the urinary tract was also present. We know that frequently abnormalities involving the urinary tract are associated with abnormalities of the genital tract. There are two types of tumors included in the term, arrhenoblastoma, one the Pick type which presumably arises from the testicular portion of an ovotestis, and one which arises from cells of the ovarian parenchyma which cells have a latent tendency to develop in a masculine direction. Such cells if stimulated possibly chemically or hormonally develop into tumors which are able to influence the host in her physical and psychic characteristics. The tumor type arising from the testicular portion of an ovotestis is composed of groups of tubules which are mature in their development as in the case presented this evening. Such tumors do not cause masculinization of the host. The second type arising from the male directed cells may cause masculinization and have a decidedly different histologic appearance. The tubules are irregular, atypical, and the main mass of the growth is a cellular spindle cell parenchyma.

DR. WILLIAM E. STUDDIFORD.—The case of a colored patient, who entered Bellevue Hospital last year with a history of two years of amenorrhea, has some bearing on this question of masculinization. Examination at the time of admission showed that she had a right-sided ovarian tumor. During the two or three years previous to admission she had grown a very large set of whiskers which she had to shave twice a day, she had deepening of the voice, and very pronounced enlargement of the clitoris. We felt quite justified in making a clinical diagnosis of arrhenoblastoma.

We removed the tumor and were very much surprised to find that it was polycystic and not solid, as most arrhenoblastomas are. After cutting a great many sections from the tumor, the only conclusion we could draw from our histologic examination was that it was a granulosa cell tumor.

Hence I am not sure you can place all these endocrinologic tumors into a definite classification as to whether they are granulosa cell tumors or arrhenoblastomas. I believe that Bergstrand in Sweden has also reported several cases similar to the one I have spoken of. He also reviewed some of Meyers' material and feels that some of these tumors are also granulosa cell tumors with masculinization.

DR. HERBERT F. TRAUT.—Dr. Miller's case is pretty clearly an instance of survival of an embryonic remnant in an individual who had originally an ovotestis. There is a predominance of the ovarian element in the tumor.

There is no question but that there are a variety of ways in which such a tumor might have arisen; survival of a portion of an ovotestis is the most important. We have other tubular tumors that arise from the blastoma type of cells, and these being more embryonic in nature, their lines of demarcation are more indefinite; arrhenoblastoma is one example of these. There is definitely a third type of tumor which may also be a tubular adenoma. This is unquestionably linked to the colonic epithelium which dips down from the cortex of the ovary into the stroma and becomes differentiated at various times. During the sex life of an individual we sometimes see it differentiated in the direction of endometriosis. Later on, after sex life is over, we see it differentiated in a number of forms, as adenomas of various sorts.

In the future we shall be able to differentiate quite a variety of adenomas of the ovary based on at least three different origins. It seems that the one which has been reviewed tonight is definitely on the side of the masculine tubules, having to do

A possible exception to this general statement may be the case reported by G. W. Phelan,³ Brooklyn, 1933. The tubules in his tumor appeared to be as highly differentiated as in the present instance though the interstitial cells were not reported. His tumor exerted a strong masculinizing effect which regressed after removal.

While Meyer agrees with Pick, Schickele⁴ and Neuman⁵ that the testicular tubules probably bespeak a true hermaphroditism, and originate in an ovotestis, yet he calls attention to the possibility that influences might transform the indifferent cells in the rete both into seminiferous tubules and Leydig cells. As Schiller⁶ has pointed out, the canalicular form, which was described by Pick, represents the highest stage of development of the arrhenoblastoma, and when an adenoma of this type (which has the greatest similarity to the testicle of all ovarian tumors) does not exert a masculinizing effect, the tissue resembles not the canalicular substance of the testicle, but the testicular rete, which possesses no hormonal action.



Fig. 6.

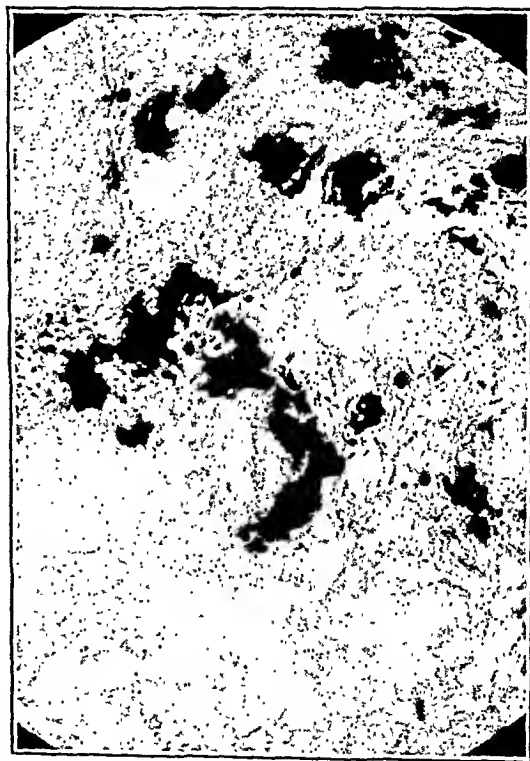


Fig. 7.

Fig. 6.—Low power. Fat shows black in photomicrograph. Frozen section, Sudan stain.

Fig. 7.—High power like Fig. 6.

From the literature, one can find no instances where this highly developed Pick tumor has become malignant. While the possibilities of malignant change must be borne in mind, such changes have been found exclusively in the less highly differentiated type of arrhenoblastomas,^{2, 5, 7} and it seemed justified to give this patient a good prognosis concerning malignancy.

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A MODIFICATION OF THE KIELLAND, SIMPSON, AND TUCKER-McLANE FORCEPS TO SIMPLIFY THEIR USE AND IMPROVE FUNCTION AND SAFETY

RALPH LUIKART, M.D., F.A.C.S., OMAHA, NEB.

THE purpose of this modification is to make the use of forceps more safe, more simple, and yet not impair their function.

It is true that "it is not the forceps but the obstetrician behind them on which the results depend," but, the nearer foolproof the instrument, the safer its use.

For years I have advised my students to purchase solid blade forceps because I have felt they are safer for the beginner. Once a proper parietal application of an obstetric forceps is made the greatest danger of damage to the fetus is due to the slipping of the forceps. This is less likely to occur if the part of the fetus between

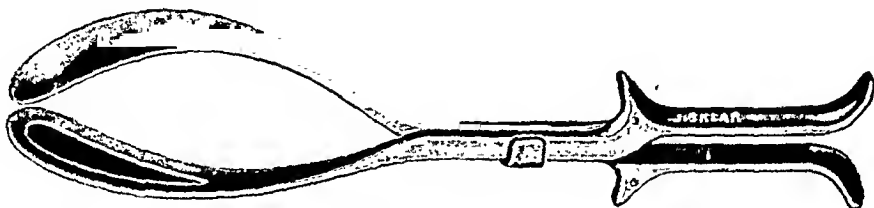


Fig. 1.—Kielland forceps.

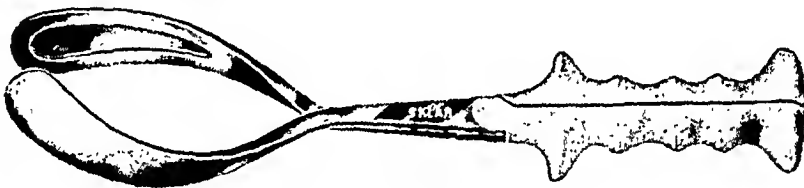


Fig. 2.—Tucker-McLane forceps.

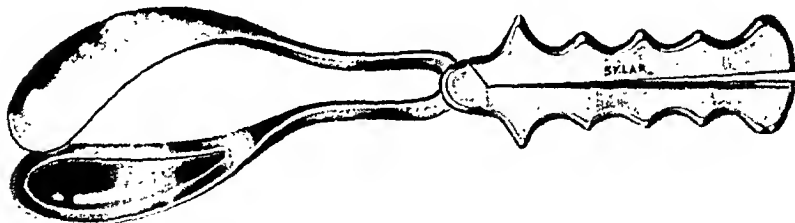


Fig. 3.—Simpson forceps.

the blades is more firmly grasped. This can only be done by greater compression of the part by the forceps. The greater compression increases the possibility of injuring the fetus. Forceps are fenestrated with the hope of decreasing the danger of the forceps slipping and at the same time using less compression. Hence, the fenestra has a definite value but there is always danger of an ear, nose, or superciliary ridge protruding through the fenestra, and then only a slight slip of the forceps may seriously damage that part.

There is no surgical instrument with a smooth surface that is used for traction except the solid blade obstetric forceps, yet traction is the prime function of obstetric forceps. Therefore, it seems logical to assume that forceps so modified that the function is improved and the application and removal is made more simple, more safe, and yet not more complicated, should be the forceps of choice. I believe the forceps here described have been so improved as to attain these desirable qualities.

with the wolffian body and its tubular system. The fact that there were a few interstitial cells is somewhat notable. They were, however, rather few in number as compared to the size of the tumor as a whole.

We must keep a very open mind in regard to the whole field of ovarian tumors and not try to pigeon-hole them too definitely. Meyer has performed a tremendous service in pointing out the embryologic origin of many of them, but there is still a great deal to be learned. If tumors do not fall into this or that category according to a specific name, we should not become discouraged, but rather should be prepared to find tumors that fit in between, all the way along, everywhere from the hilum of the ovary to the ovarian cortex, from all types of cells and in every stage of differentiation.

DR. GERARD L. MOENCH.—When you look at an ovary in its development you will find that the ovary is differentiated from the testis long before you can tell whether the fetus is male or female from the external genitals. One of the differentiating points is the presence of the sex cells in the ovary, but the stroma cells themselves are practically the same. In fact, these cells, which are more or less indifferent, give rise later to the peculiar type of tumor, the dysgerminoma or large cell carcinoma. An ovotestis is not related to these arrhenoblastomas in any way.

If you have testicular tubules, you find that at body temperature, that is, in the abdominal cavity, they will always lack epithelium. They will be present simply as hyaline degenerated tubules. The very fact that we have epithelium here shows we are not dealing with an ovotesticular structure, but with something which begins or starts before any testicle is laid down. It is not surprising when we consider their derivation, that the more the tubular structures develop, the less the masculine characteristics of the tumor are present, because masculinization is not dependent on the tubules, but on the interstitial cells.

These arrhenoblastomas will be divided into those tumors which show definite tubular structures, those which show some tubular structures, and those which show practically nothing but a diffuse growth which might lead back to the original stromatogenous cells of the ovary. For this reason it is not very surprising that some of the granulosa cell tumors and some of the arrhenoblastomas of the indifferent type look very similar, because in the original gonadal development, these cells look very much alike.

I feel we have to distinguish here between tumors which are derived simply from remnants of what one might say are abnormal developments of the testicular anlage, and those which are developed from undifferentiated cells and which possibly for one reason or other change, toward the testicular side, rather than toward the normal ovarian side.

DR. JAMES R. MILLER.—It is premature to try to settle this complicated question on the basis of one case, but by placing cases on record one can get a series and possibly in the future come to some better conclusion.

Freiman, S. C.: The Interstitial Glands in Human Beings, *Monatschr. f. Geburtsh. u. Gynäk.* 104: 224; 1937.

The author studied the ovaries obtained in 100 cases from the fourth month of embryonic development to the sixtieth year of life including 4 pregnant women. He found definite elements of interstitial glands in only 6 of these cases. No glands were found in any case after the sixteenth year.

J. P. GREENHILL.

Department of Practical Problems in Obstetrics and Gynecology

CONDUCTED BY WILLIAM J. DIECKMANN, M.D.

THE TREATMENT OF FUNCTIONAL UTERINE HEMORRHAGE

FLOYD E. KEENE, M.D., AND FRANKLIN L. PAYNE, M.D.,
PHILADELPHIA, PA.

ABNORMAL uterine bleeding is ascribed to a functional origin when the pelvic organs are normal and when no constitutional disease or blood dyscrasia exists to account for it. The modern conception of its etiology recognizes an alteration from the normal functional relationship between the hypophysis, the thyroid, the ovaries and the endometrium.

Functional bleeding occurs most commonly during the fifth decade of life, but it is encountered frequently in women of less mature years in whom preservation of the menstrual and procreative functions is of vital importance. In many of the milder forms, the blood loss is insufficient to require treatment, as is often the case in adolescence. The same may occur during the menopausal age, but here the more likely cause of irregular bleeding is a myoma or cancer and hopeful expectancy is warranted only when the possibility of these organic lesions has been eliminated.

The wide age distribution of functional bleeding necessitates a variation in the objectives of its treatment. If we could devise an ideal therapeutic method, it would have for its result preservation of the normal menstrual and procreative functions in women under forty, and the return to normal periods or amenorrhea without severe menopausal symptoms in women beyond this age. Unfortunately, the methods at our disposal often fall short of this ideal, but in our choice of treatment, we should attempt to approach it as nearly as possible. Only too often methods are employed with the control of bleeding as the only objective and with entire disregard of the disastrous sequelae which may accompany the destruction of ovarian or reproductive function. Proof that the ideal treatment of functional bleeding has not been found is the large number of therapeutic procedures which have been and are still being introduced. These methods may be divided into seven groups: (1) Hygienic measures. (2) Uterine stimulants. (3) Means to increase the coagulability of the blood or to decrease the permeability of the capillaries. (4) Endocrine therapy. (5) Removal or destruction of the endometrium. (6) Roentgen or radium therapy. (7) Surgical procedures upon the ovaries or the uterus.

Hygienic measures are of value when used in conjunction with appropriate medical and glandular therapy. Constitutional defects often

The modification consists of a change only in the design of the blade of the forceps so that the pelvic surface is smooth, as is the case in any solid blade forceps but the fetal surface of the blade has a depression similar to the fenestrated forceps. In short, it is a fenestra with the pelvic side closed. In the case of the Tucker-McLane forceps a depression similar to a fenestra has been made in the fetal side. The pelvic surface of the blade appears unchanged. The weight of the forceps is practically unchanged. The application and removal is made with greater ease and most important, the safety is definitely increased.

COMMENTS

1. In 1851 Smellie recognized the need for such a modification of forceps with fenestrated blades. He covered the blades with leather.

2. Standard Kielland forceps, weight $9\frac{1}{4}$ ounces, 10 grains. Plated Kielland forceps, weight $10\frac{1}{2}$ ounces. Tucker-McLane forceps, weight $13\frac{5}{8}$ ounces.

1530 MEDICAL ARTS BUILDING

TETANUS ASSOCIATED WITH CRIMINAL ABORTION

GEZA G. KOMAROMY, M.D., CLEVELAND, OHIO

DURING recent years various observers have reported the incidence of tetanus infection, which developed after criminal abortion. It is essential, however, to determine whether the inoculation of this organism took place through other wounds of the skin as it is possible that the tetanus was merely co-incidental with an abortion.

The following report concerns the case of a white woman, forty-two years of age, seen Nov. 10, 1935. She had three children, all living and well, and her previous history was negative. Her complaint was difficulty in breathing, swallowing, and a backache. These symptoms began one day previous to my seeing her. Next day when I saw her for the first time, she had a dull pressure in the chest and precordial pain. She could not open her mouth fully. Examination showed nothing abnormal in the abdomen or pelvis. There had not been any scratches or injuries on the body. There was no fever. On admission to St. Luke's Hospital the following day, the temperature was 37.8° C., pulse 100. She presented a moderate degree of trismus and opisthotonus. Urine and blood examination were practically negative. The patient admitted that a criminal abortion had been performed by a midwife nine days prior to admission to the hospital. When examined in the hospital nothing was found except a slight enlargement of the uterus. There was a consultation with Dr. Skeel, Chief of the Obstetrical Staff, and with Dr. Nichols from the neurologic department. Their opinion was also that the tetanus infection developed from the criminal abortion.

Twenty thousand units of antitetanus serum were given intravenously and a dose of equal size intraspinally. No reaction occurred. Later 750 c.c. of normal saline solution was administered. By evening the pulse became irregular, the respiration increased, and the patient became quite excited. The next morning she expectorated a large quantity of thick sanguineous sputum. There was cyanosis and dyspnea with marked trismus and opisthotonus. The temperature was 39.9° C., pulse rapid and irregular. Within a few hours a severe general convulsion occurred, followed by death.

periods. Although older patients often respond, Watkins has pointed out that the results in adolescent hemorrhage are the most satisfactory.

Cevitamic acid, which is the active principle of vitamin "C," has been used in German clinics for some time. Fifty milligrams of cevitamic acid approximately corresponds to the active vitamin "C" in 100 c.c. of fresh orange juice. Marked deficiency in vitamin "C" results in scurvy with its hemorrhagic manifestations. According to Albrecht, cevitamic acid prevents dissolution of the endothelial cells, thereby decreasing the permeability of the capillary walls. Schroeder found a prolongation of the coagulation time in vitamin "C" deficiency. It seems that cevitamic acid acts upon the blood and the blood vessels. The technique of administration consists of the daily intramuscular or intravenous injection of 50 mg. of cevitamic acid in an isotonic saline solution. According to the reports, this usually checks profuse uterine bleeding within four to six days. Junghaus reported 35 patients with preclimacteric bleeding, of whom 33 were relieved. A total of 46 cases was collected from the literature with 43 (93 per cent) satisfactory results. While age does not seem to influence the results, the majority of the patients in this series were in the climacteric era.

Intravenous injections of Congo red have been used for the control of venous bleeding of various types, including uterine hemorrhage. Rossak found that these injections resulted in an increase in thrombocytes and a decrease in the coagulation time of the blood. Graves and Kiekham recently reported a series of urologic patients in whom Congo red was effective in controlling acute bleeding in the presence of normal blood coagulability. The recommended dose is 5 to 10 c.c. of the sterile isotonic solution administered intravenously. A single injection often checks the bleeding or several injections may be necessary at two- to three-day intervals. Of 30 patients with functional bleeding who have been reported, 21 (70 per cent) responded to the injections, 5 (17 per cent) were partially relieved, and 4 (13 per cent) were not benefited. The drug seems to be effective even in the absence of blood dyscrasia but recurrences of the bleeding are common.

The clinical use of parathyroid extract, which is usually given in conjunction with calcium, was made practical by Collip. Its use in functional bleeding is suggested by the fact that this hormone renders available large quantities of calcium which is necessary to the coagulation of blood. Bakács reported 87 patients, 66 (72 per cent) of whom stopped bleeding in three or four days following the daily injection of 50 Collip units of parathormone in conjunction with calcium. He states that the succeeding periods were often "favorably influenced." Of 103 cases collected from the literature, the bleeding was checked in 73 (71 per cent), partially controlled in 20 (19 per cent), and unaffected in 10 (10 per cent). While the immediate effects are usually good, recurrences are common, rendering parathyroid extract ineffective as a curative measure.

Blood transfusions are often of value in the treatment of severe functional bleeding. Not only do they combat the anemia, but in some instances they are curative in that cessation of bleeding and a return to the normal menstrual flow may follow a single transfusion. Just why this should occur is not understood. Such a happy result in our experience has occurred only in the menstrual irregularities of adolescence.

are attended by disturbances in endocrine function which are expressed by abnormal uterine bleeding. For instance, Lawrence emphasizes the importance of dietary deficiency, particularly improper nitrogen balance, correction of which may result in the return of normal menstruation. As is well known, irregular bleeding may accompany severe secondary anemia and often responds quickly to correction of the anemic state. Again, focal infection may be a factor in reducing the constitutional stability of the individual with an increased tendency to abnormal uterine bleeding. A common experience is the frequent alteration in menstruation with either the development of abnormal hemorrhage or a return to normal periods which follows a change in vocation, climate, or environment.

Uterine Stimulants.—Various uterine stimulants have been recommended in abnormal uterine bleeding under the assumption that it is due to faulty contractibility of the uterine muscle incident to malposition, chronic subinvolution, or inherently poor muscle tone. Diasio reports excellent results from the use of ergotamine tartrate. Extracts of hydrastis have been used as uterine stimulants for years. The most active is hydrastinine hydrochloride which, according to Cushny, stimulates rhythmical and powerful uterine contractions. Cotarmine chloride (styptieine) has a similar action, but according to Cushny is inferior to hydrastinine. Favorable results have been reported by Martzloff from the use of pituitrin during active bleeding, and VanderHoeven found that adrenalin chloride checked the bleeding in a small number of patients. German gynecologists have used breast stimulation to check uterine bleeding. This is practiced by galvanic stimulation as recommended by Cronental, or by mud packs applied to the breasts and to the pelvic region (Strawomysolow). Intravaginal ultraviolet therapy is recommended by Handeker who combines this with the administration of calcium and the anterior pituitary-like hormone. It is our belief that the condition of the uterine musculature has little or nothing to do with abnormal uterine bleeding except in the case of the subinvolution following pregnancy.

Blood Coagulants and Endothelial Stimulants.—Substances which affect the coagulability of the blood or the permeability of the capillary walls have been added recently to the list of therapeutic agents in functional bleeding. Moccasin venom was introduced by Peck and Goldberger in 1933. Peck believes that the results are due to changes in the vessel walls or to some effect upon the clotting factors of the blood. The technique of administration, as advised by Goldberger, consists of the subcutaneous or intramuscular injection of the 1 to 3000 dilution of moccasin venom. The initial dose should be 0.5 c.c., increased to 1 c.c. by the third day. As much venom as possible is administered during the first ten days, because sensitivity necessitating desensitization often develops at the end of that time. Daily injections of 1 c.c. are given during the active bleeding to be decreased to two or three injections a week after the bleeding is controlled. Goldberger obtained satisfactory results in 17 of 20 patients so treated. Of 47 cases collected from the literature, the bleeding was controlled in 42 (90 per cent). Recurrences, which are frequent, usually respond to the second series of injections. The treatment should be continued through three menstrual

effect is exerted upon some unknown bleeding factor," which seems to be "bound up with a disturbance in the balance between the two anterior pituitary hormones." Smith and Roek suggest a direct action upon the hypophyseal secretion. In view of the fact that immediate cessation of the bleeding at times follows the injection, one must assume that the effect is produced substitutionally and is not due to a modification of ovarian or pituitary function.

The anterior pituitary-like hormone may be administered in several forms. Prior to the introduction of more potent urine extracts, sterile urine of early pregnancy was injected intramuscularly with good results as to bleeding but with frequent, severe local reactions. Tachezy, and Warehowsky administered urine from pregnant women per rectum in 14 cases, in all of which the bleeding was controlled. Blood from pregnant women or blood serum has been found effective in 87 per cent of 84 patients by Clauherg and by Witherspoon. The prolan extracts now available for clinical use are derived from the urine of pregnant women or from the placenta (Collip). In 483 collected cases, satisfactory results were obtained in 347 patients (71 per cent), 35 (8 per cent) have been partially relieved or have had recurrences and 101 (21 per cent) have been unaffected. The largest single series consisted of 78 patients reported by Campbell who used the placental extract and controlled the bleeding in 72 (92 per cent). His patients were grouped according to the type of bleeding, irrespective of age. He found the response inconstant in metrorrhagia of puberty, and saw no permanent improvement in simple polymenorrhea of any age. In contrast to this, Smith and Roek reported 56 patients from seventeen to forty-two years of age, in whom urine prolan was found to be more effective in the menorrhagias, regardless of the age.

In our experience, the best results were obtained in the younger patients irrespective of the type of bleeding. Of those less than twenty, 78 per cent responded satisfactorily; 73 per cent of the twenty to thirty-year group recovered; and in 67 per cent of those between thirty and forty, the bleeding was controlled. We rarely employ prolan therapy in patients after the age of forty, because we have found that it is usually ineffective, at best being only of temporary benefit, more drastic measures becoming necessary sooner or later. Of the 168 patients whose ages were stated in various reports from the literature, 74 per cent of the adolescents and 58 per cent of those from twenty to thirty years of age were satisfactorily affected. In the thirty- to forty-year group, 72 per cent were relieved, and only half of those from forty to fifty years of age.

Slight variations in the technique of treatment are met in different clinics. Since patients usually seek advice while bleeding, the authors begin treatment by injecting 200 rat units or 200 biologic day units (Collip) daily until the bleeding ceases or until ten injections have been given. With cessation of the bleeding, the dose is reduced to 100 units every third day until the next period starts, when the original dose is resumed and continued through the period. The smaller dose is then given until the time for the second period, when the treatment is concluded. Recurrences are seen occasionally and these usually respond to the second series of injections. Our experience has been more satis-

Endocrine therapy.—Since functional bleeding is caused by abnormal endocrine activity, practically all of the glandular products have been given a trial in its treatment. Drips in 1934, reported improvement in 71 per cent of 94 patients from the use of estrin (sistomensin). Recently Siebke has found that approximately half of his patients responded to estrin therapy. Estrin in large doses may delay uterine bleeding temporarily, but its curative value is doubted by all gynecologic endocrinologists. Klawns reported 48 cases of functional bleeding, many of the patients with diabetic backgrounds, in 32 of whom bleeding ceased following the use of insulin and high carbohydrate feedings. He pointed out that recurrences are frequent and more likely to occur as the age of the patients advances.

Theoretically, corpus luteum extracts should be of value in the treatment of functional bleeding, but until recently potent extracts have not been available for clinical use. It is supplied in ampules which vary in content from $\frac{1}{25}$ to 1 rabbit unit. Kauffman was able to produce a premenstrual endometrium in a castrated woman with 50,000 rat units of estrogenic substance followed by 35 rabbit units of proluton. That such endometrial transformation follows the small doses of progestin now in vogue is questionable. As Wilson and Elden suggest, however, with the ovaries in situ possibly a certain amount of progesterone is produced in follicles undergoing atresia, and this may be supplemented by its hypodermic administration. These authors controlled abnormal uterine bleeding in 5 patients with hyperplasia with total doses of progesterone varying from $\frac{2}{25}$ up to $1\frac{15}{25}$ rabbit units. They did not study the endometrium after treatment and concluded that "for the present the dosage will have to be along empirical lines." The permanency of the results is open to question as the therapy is substitutional and recurrence of bleeding will probably follow cessation of the injections.

Functional hemorrhage is often associated with various degrees of hypothyroidism. Plass pointed out the value of thyroid therapy in adolescent hemorrhage even in the absence of definite evidence of deficient thyroid function. In a study of 59 patients with myxedema, Gardiner, Hill and Smith found menorrhagia to be a common complaint, even as late as the premenstruum. The exact effect of thyroid is not known, but it seems to aid in regulating the rhythm of the gynecologic-endocrine cycle. It is usually administered in conjunction with other endocrine products, particularly the urine or placental prolactin extracts.

The initial dosage of thyroid is governed by the basal metabolic rate and the clinical status of the patient, varying from 0.5 to 1 gr. a day. Every two weeks the dose is increased 0.5 gr. a day until the patient's level of tolerance is reached, as evidenced by her nervous reaction, tachycardia, dyspnea or loss of weight. The thyroid is then discontinued for two weeks, to be resumed in two-thirds the last dose and maintained at that level. It is continued for at least three months before it is judged ineffective and if satisfactory results occur, it should be administered even longer.

In 1931 Novak and Hurd reported cessation of bleeding in 44 of 51 patients who were treated by the injection of urine prolactin extract. The action of this substance is not known. Geist, and later Hamblen and Ross have proved that it does not cause luteinization of persistent ovarian follicles. Hamblen has shown recently that endometrial hyperplasia is unaffected by large doses of prolactin. Novak suggests that "the

tients with functional bleeding who were treated by splenic irradiation alone, and the bleeding was relieved in only 42 per cent.

The most common form of irradiation therapy is that applied to the ovaries and uterus and when properly used, this is a safe and effective method of treatment. Its harmful effects depend upon disturbance in the secretory function of the ovaries and in alteration of the ova so as seriously to affect subsequent pregnancy. Murphy has shown that pre-conception irradiation does not predispose to abnormal offspring or to miscarriage. He has further shown experimentally that the first effect of irradiation upon the maturing ovum is to render it incapable of fertilization. Murphy's view, however, is not universally accepted, and evidence is available to indicate that irradiated ova may suffer permanent damage and yet not be rendered unfertilizable. Our personal experience confirms Murphy's statement in that offspring following radium irradiation have without exception been normal.

Review of the literature shows that x-ray irradiation of the ovaries is satisfactory so far as control of the bleeding is concerned, but little could be found bearing upon the incidence of permanent amenorrhea and severe menopausal symptoms produced by this treatment. Our own experience has been limited, since this form of therapy has been reserved for patients in whom intruterine radium is contraindicated.

Radium Therapy.—We prefer radium because its dosage can be regulated more delicately and the beneficial effects are in part due to its local action upon the uterine blood vessels. Further, with radium, completion of the treatment is accomplished at the time of the diagnostic curettage which should precede either form of irradiation in most instances. It deservedly occupies a prominent place in the treatment of functional bleeding, and in women of menopausal age it approaches the ideal. It has also proved of value in younger women, but here one must appreciate its limitations and dangers if disastrous sequelae are to be avoided. Since the cure of bleeding by radium is accomplished largely through its effect upon ovarian function, an evaluation of radium therapy must take into consideration not only the control of bleeding but also the manifestations which have arisen incident to disturbance of this function.

CONTRAINDICATIONS TO RADIUM

Profoundly anemic patients react poorly to both radium and roentgen therapy and either form of irradiation should be withheld until the blood has been improved by transfusion and other appropriate treatment.

Pemberton has called attention to the danger of radium in patients who have had a previous pelvic operation, since an intestinal loop adherent to the uterus may be seriously damaged by the rays. In a few such instances we have given short applications of heavily filtered radium successfully, but we prefer operation or roentgen therapy.

The absence of intermenstrual pelvic pain and severe dysmenorrhea is characteristic of functional bleeding. When pain is an associated symptom, some organic lesion is usually present, even though examination fails to reveal it, and operation is preferable to radium therapy. With surprising frequency the wisdom of this decision will be proved when the abdomen is opened.

factory with the placental extract (Collip) than with the urine extracts, although the former is more likely to cause local or mild constitutional reactions.

Destruction or Removal of Endometrium.—The modern conception of the causes underlying functional bleeding would seem to cast discredit upon curettage and other methods of removing the endometrium, but the fact remains that satisfactory results have been reported from the use of such measures. Holzapfel advocates steam vaporization of the uterine cavity and reports excellent results in 111 patients although 2 of them died. A small two-way cannula is placed in the uterus and steam at a temperature of 125 to 130° C. is applied for one minute. This is followed by a short rest, and the procedure is repeated four or five times at one sitting. He warns that the vaginal walls must be well protected by gauze sponges and the escape of the steam must be unhampered. A second method of endometrial destruction is the use of zinc chloride in solution or in pencil form. Vorster treated 100 cases with zinc chloride pencils and obtained satisfactory results in all. He states that a moderate febrile reaction occasionally follows the treatment, and a profuse discharge persists for some time. The intrauterine application of a diathermy pencil is recommended by Theilhaber. With the indifferent electrode on the abdominal wall, a vulcanite uterine sound is heated until it causes blanching of the vaginal lining. At this point it is introduced into the uterine cavity and the current is applied for fifteen seconds. One hundred and fifty-eight young women were treated by this method with no untoward reactions and his results were "always satisfactory." We have no personal experience with such measures, and they are mentioned only to be condemned. We consider them unsound, and they are likely to be attended by disastrous sequelae.

Curettage still holds an important position in the diagnosis and treatment of functional bleeding. C. Jeff Miller was a firm advocate of repeated therapeutic curettage in adolescent hemorrhage. Geist and Glassman recently reported 142 patients in whom this procedure produced satisfactory results in 52 per cent, partially satisfactory in 12 per cent, and no relief in 36 per cent. Except in adolescents, they recommended that the initial therapeutic step should be a simple curettage, and they point out that a cure is unlikely in the presence of endometrial hyperplasia. This belief is confirmed by Martin's figures of 64 per cent recurrence of bleeding in 94 patients with hyperplasia who were treated by curettage alone. Our experience with curettage has been disappointing. Whatever benefit may accrue is temporary, recurrences taking place in more than half of the cases within two months.

Irradiation.—Irradiation has become a widely used method of treating functional hemorrhage and in patients of the menopausal age pelvic irradiation approaches the ideal. It is also of value in women of less mature years, but it must be used with the greatest caution because of its effect upon ovarian function. Roentgen irradiation has been applied to the pituitary gland, the spleen, and the ovaries, alone or in combination. From a review of the literature, it is impossible to evaluate the results of pituitary irradiation alone, because it has been used almost invariably in combination with irradiation of ovaries or spleen. Several years ago, splenic irradiation had many advocates, but the paucity of recent articles dealing with this method of treatment indicates its loss of popularity. We collected from the literature 188 pa-

develop a temporary amenorrhea of a few months' duration. Should the bleeding persist, the dosage can be increased by 100 mg. hours.

Our analysis of the group between thirty and forty brings out the important fact that with increasing dosage there is a rapidly increasing incidence of menopausal manifestations. With a dosage of between 800 and 1,200 mg. hours, permanent amenorrhea occurred in 56 per cent and severe menopausal symptoms in 47 per cent of the patients. An initial dosage of 300 mg. hours will control the bleeding in 80 per cent and without permanent amenorrhea. Should re-radiation be necessary, an application of not more than 400 mg. hours should be administered and if this fails, we favor hysterectomy with conservation of ovarian function rather than increased irradiation.

Functional bleeding occurs most frequently between forty and fifty years of age, and because these women are approaching the time when, in the normal course of events, functional activity will cease, the administration of a menopausal dose of radium has come into common usage. We believe this is a mistake because of the high incidence of severe menopausal symptoms. In women near forty, we are using a 400 mg. hour dosage. Should this and a re-radiation dosage of 500 mg. hours fail, a hysterectomy is advised. In women near fifty years of age, increased radium dosage can be used because the incidence of severe menopausal symptoms attending it will more nearly approximate that of the uninduced menopause.

Between fifty and sixty years of age, the results of radium therapy approach perfection. Maximum dosage can be given, since severe menopausal reactions rarely develop.

OPERATIVE PROCEDURES

Hysterectomy is reserved for those patients who have not responded to less radical measures or those in whom irradiation is contraindicated. From our experience, we are convinced of the value of ovarian conservation since with it the incidence of severe menopausal symptoms is almost negligible. High amputation of the uterus or wedge-shaped excision of the fundus, according to the Bell-Benttner technique, has been advocated. These procedures are desirable in that menstrual function is continued. On the other hand, bleeding of the functional type is often prolonged and irregular and while these methods reduce the quantity of the flow, they do not assure its regularity.

In the presence of functional bleeding, the ovaries frequently contain single or multiple follicular cysts. The results of excision of a single cyst, the puncture of multiple small cysts or unilateral oophorectomy without hysterectomy are so uncertain in their effect upon the bleeding as to make them inadvisable. The same is true of partial resection of a polycystic ovary. Since these lesions are the result of faulty endocrine function, such procedures are theoretically fallacious and are practically useless.

SUMMARY AND COMMENTS

The large number of proposed methods indicates that no uniformly satisfactory treatment for functional bleeding has been found. In pre-climacteric bleeding, satisfactory results follow irradiation or surgical ablation. Before and during the reproductive ages the maintenance of menstrual and reproductive functions demands a trial of less radical

The highly nervous woman is ill adapted both to radium and roentgen therapy because of the distressing sequelae which frequently attend the induced menopause. In this type of woman, hysterectomy with ovarian conservation yields better results.

Technique of Application.—We prefer general anesthesia because it permits a more accurate pelvic examination. The uterine cavity is explored with a sound and a curette in order to eliminate an organic lesion such as retained secundines, pedunculated submucous tumors, or carcinoma. The length of the uterine cavity is measured and 50 mg. of radium, filtered with 1 mm. of platinum, is encased in a soft rubber tube 2 mm. in thickness and of a length corresponding with that of the uterine cavity. The radium should be in the top of the uterus. In order to prevent slipping of the rubber tubing, the external end is sewed to the anterior lip of the cervix as advised by Furniss. As an added safeguard, the vagina is packed. When the radium is to be in place for eight hours or more, a permanent catheter is placed in the bladder. The patient remains in bed for two or three days and is usually sent home on the fourth day. In properly selected cases, the intra-uterine application of radium is attended by no mortality and a minimum of morbidity. Nausea and vomiting commonly occur so long as the radium remains in the uterus, but they rapidly subside with its removal. During the earlier years of our experience, when the radium was filtered inadequately, a persistent and annoying leucorrhea was a common sequel. This has been eliminated almost entirely by the filtration now employed.

Dosage.—The initial dosage of radium is of paramount importance. This decision depends not only upon the incidence of controlled bleeding which can be anticipated from a given dosage but also upon the incidence of amenorrhea and severe menopausal symptoms which may follow this dosage. A study of our results emphasizes certain general principles which are pertinent. Individual variation in susceptibility to the effects of radium is not uncommon and, for obvious reasons, this fact is of importance in treating young women. When analyzed in groups and by decades, our findings suggest that between twenty and thirty years of age the ovaries are resistant or they possess a strong recuperative power; for in not a single instance did a permanent amenorrhea develop despite the fact that some of these patients had been given a fairly large dosage. Increased susceptibility to radium begins after thirty and gradually increases, reaching its height in patients who continue to menstruate after fifty. Further, the incidence of permanent amenorrhea and severe menopausal symptoms runs parallel until forty when as amenorrhea increases with a given dosage of radium, severe menopausal symptoms decrease until between fifty and sixty the incidence of these symptoms is almost negligible.

From our study of the effects produced by varying initial dosages during the different decades, we have drawn conclusions which govern us in our work and these will be summarized briefly:

Radium is rarely indicated in the treatment of patients under twenty years of age. When it is found necessary, the initial dosage should not exceed 200 mg. hours.

Between twenty and thirty, our results show that a dosage of 400 mg. hours can be administered safely. This dosage will be more than 80 per cent efficient in the control of bleeding, but a few patients will

Society Transactions

NEW YORK OBSTETRICAL SOCIETY

MEETING OF FEBRUARY 9, 1937

The following papers were presented:

Worth-While Surgery in the Newborn. Dr. James A. Harrar. (For original article, see page 661.)

Incontinence of Urine in the Female, the Urethral Sphincter Mechanism, Damage of Function, and Restoration of Control. Dr. William T. Kennedy. (For original article, see page 576.)

The Bissell Operation for Cystocele. Dr. Hermann Grad. (For original article, see page 589.)

MEETING OF MARCH 9, 1937

The following papers and discussions were presented:

Testicular Tubular Adenoma (Pick). Dr. James R. Miller. (By invitation.) (For original article, see page 680.)

Methods and Results of Treatment in Carcinoma of the Cervix at the Memorial Hospital. Dr. William P. Healy and Dr. E. L. Frazell. (For original article, see page 592.)

The Effect of Pregnancy on Malignant Tumors. Dr. Frank R. Smith. (For original article, see page 616.)

BROOKLYN GYNECOLOGICAL SOCIETY

MEETING OF FEBRUARY 5, 1937

The following paper was presented:

The Vascular Factor in the Toxemias of Late Pregnancy. Dr. Nicholson J. Eastman, Baltimore, Md. (For original article, see page 549.)

measures. The blood coagulants are moderately successful in checking the bleeding but recurrences are common. Snake venom offers promise of satisfactory results. The ideal endocrinotherapeutic substance, which has not yet been produced, would stimulate normal ovarian rhythm, thereby causing normal endometrial changes. The present hormone therapy in the form of urine or placental prolan and corpus luteum extracts is purely substitutional. The administration of thyroid extract, alone or in conjunction with other endocrine products, is usually advisable. Use of the luteal hormone is still in the experimental stage as to both dosage and permanency of results. Prolan therapy when administered to young women is effective in approximately 75 per cent of the cases.

Of the less radical surgical procedures, enrettage is harmless and may be curative. Irradiation, when directed to the spleen, is moderately successful in checking the bleeding but is of little permanent value. Adequate ovarian roentgen irradiation controls the bleeding but carries with it the danger of a premature menopause. Intrauterine radium, in properly regulated doses, is generally effective without permanent alteration of the menstrual or reproductive function.

The authors believe that functional bleeding of the preclimacterium should be treated by enrettage and the immediate application of intrauterine radium. During adolescence and middle life, hormonal and other forms of conservative therapy should be given a trial. Should this fail, enrettage with or without the application of radium, depending upon conditions, is indicated. If radium is used, due regard should be given to its contraindications and to cautious regulation of the dosage. Hysterectomy with ovarian conservation is indicated when other methods have failed or when some contraindication to irradiation exists.

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the interval state, they found in the majority of instances the Ca to vary between 11.6 and 12.8 mg. per cent, of K between 19 and 27 mg. per cent, the relation between K and Ca being 1.4:2.1. Premenstrually the Ca often rises, but not above normal levels, while at the same time the K becomes lower, changing the relation of K to Ca to 1.29:1.91. In the few observations made during the flow, the relation of K to Ca was 1.03:2.1.

Noteworthy *calcium* changes in connection with the menstrual function, on the other hand, are denied by Matters and Hnebbe,⁹⁴ who emphasize that their results coincide with the more recent findings of various German investigators. In an article on blood chemistry Pucher and others⁹⁵ state that blood *cholesterin* rises in the week after the flow, that *calcium* is highest during the flow, and that there is a noticeable increase of *chlorides*, *uric acid*, and *creatinine* during the bleeding.

In connection with *cholesterin* changes in the blood, we might here refer to observed lipid changes in the endometrium. In a discussion of the *lipoid* contents of the endometrium, Gohlisch⁹⁶ mentions that Bellini found lipoids in larger quantities only during the intermenstruum, diminishing in the premenstrual stage. Weishaupt and Froboese failed to ascertain any change in lipid contents connected with the menstrual cycle. Aschheim observed that large quantities appear in the premenstrual endometrium and Gohlisch now confirms these latter findings.

Fukase⁹⁷ investigated *bilirubin* variations in the blood serum of healthy nurses. There is a definite increase premenstrually with fall at the onset of the flow. He found this was most marked in girls who menstruated regularly, had a moderate blood loss, and only slight subjective symptoms.

A paper of De Lisi⁹⁸ deals with the relation of *adrenalemia* to menstruation. The adrenalin contents of the blood are the highest just before the flow and drop with its beginning. He emphasizes the striking parallelism between adrenalin and blood pressure curves. Another Italian investigator, Barbera,⁹⁹ found that in healthy, normally menstruating girls, between nineteen and twenty-eight years old, there is consistently a rise of blood pressure between 2 and 7 mm. Hg on the day before the flow which disappears with the start of the flow.

Garni and Ruggeri¹⁰⁰ made 1034 *blood sugar* determinations on 93 women with normally functioning genitalia and 41 women with gynecologic disturbances. The lowest levels were always encountered in mid-interval. There follows a gradual rise with temporary fall within fourth or fifth premenstrual day and a new rise at its peak at time of start of flow. Gradual fall begins on the third day of the flow down to minimum concentration on the twelfth day. These changes are most marked in normal, healthy women but may become rather irregular in the presence of gynecologic ailments.

Eufinger¹⁰¹ ascribes the increased blood sugar level in connection with the menstrual flow to increased transformation of glycogen into blood sugar expressed in a lowering of *glycogen* contents. However, Kinoshita¹⁰² denies any consistent alterations of the blood sugar levels in connection with the menstrual cycle. Noteworthy in this connection are the studies of Higuchi and Yamashita¹⁰³ who found the premenstrual endometrium to contain large amounts of glycogen while only traces can be discovered in the mucosa of the interval.

Department of Reviews and Abstracts

CONDUCTED BY HUGO EHRENFEST, M.D.

Collective Review

MENSTRUATION AND ITS DISORDERS

A CRITICAL REVIEW OF THE LITERATURE FROM 1933 TO 1936 INCLUSIVE

HUGO EHRENFEST, M.D., ST. LOUIS, MO.

(Continued from page 530, September Issue.)

VIII. CONSTITUTIONAL CHANGES

By constitutional changes we mean those general systemic changes that occur in association only with true menstrual flows of the ovulatory type.

A. *Blood*.—Leverton and Roberts⁸⁸ made a study of the *iron metabolism* on four normal, healthy college girls observed through several successive periods and kept on a constant diet. In the course of three months in each of them, there were ascertained daily variations in *hemoglobin* contents, but these variations were not found to be dependent in any way upon cyclic ovarian activity. Similar are the conclusions of Christianna Smith,⁸⁹ who made daily *hemoglobin* determinations on several healthy women, also studied the number of *erythrocytes* and *reticulocytes*, and the *red cell volume*. She found variations within narrow limits but no influence of the menstrual cycle on them.

According to Kato,⁹⁰ the number of *blood platelets* begins to increase in the premenstruum and decreases again with the onset of the flow, the lowest figures being found on the second day. If the flow lasts several days, the number of platelets again increases before the flow has stopped. In the intermenstruum, the platelets are at the normal level.

Interesting observations on marked changes in *leucocyte* contents of the blood are recorded by Jackson and Merrill⁹¹ in a report of recurrent attacks of agranulocytic angina. This and similar cases we shall discuss later in detail.

Tuthman and Grass⁹² observed definitely cyclic changes in the *arsen* contents of the blood expressed in a gradual but considerable increase with approach of flow time. The lowest level occurs in the intermenstruum. They claim that the average level is more or less constant for the individual but differs between different individuals. In their opinion, this premenstrual increase of arsen in the blood expresses preparation for pregnancy, because if it actually takes place there is a further increase.

The calcium and potassium contents of blood serum were investigated by Schepetinsky⁹³ on a number of normally menstruating women. In

saline solution to concentrations between 1:1000 down to 1:100,000, and then permitted to dry slowly on a glass slide. Crystalline figures thus forming are irregular from blood taken during the intermenstruum, but are increasingly more concentrically regular the nearer to the expected next flow the blood is obtained. In the postmenstruum the figures become starlike. These changes in crystallization were proved to be dependent on endocrine changes by means of experimental administration of either follicular or anterior pituitary hormone.

In this connection, we may refer to the claim of Selous and Perryman¹⁰⁹ that during the flow period the *surface tension* of the urine becomes much lower. They feel unable to state which particular constituent is responsible for this change.

Hubert¹¹⁰ investigated 16 different biologic functions on 6 normally menstruating women, all active in different occupations. More or less marked variations were noted in regard to weight, temperature, systolic blood pressure, pulse pressure, pulse rate, size of thyroid, all controlled daily, and of hemoglobin, red and white cell counts and red cell sedimentation time, all controlled four times within a cycle. With the sole exception of the sedimentation time, none of all the other changes could be brought into direct connection with the particular cycle phases and more likely seemed dependent on other external factors.

B. Edema.—In 1933, Thomas¹¹¹ reported two cases in which only at the time of the menstrual flow a marked edema developed coincident with headache, blurred vision, and noticeable congestion in the eye-grounds. In one of the two women, the results of administration of anterior pituitary-like urinary extract were "spectacular." The edema did not appear at all or was only very slight. A similar observation of "edema of unknown origin during menstruation" was described by Molnár.¹¹² This girl, twenty-two years old, suffering from a pulmonary tuberculosis, developed just before or with the onset of flow an edema of the face and on both lower extremities up to the knees. It was ascertained that with the approach of flow time there occurred a gradually increasing retention of water and sodium chloride, manifesting itself in an hyperchloremia and marked hypoalbuminosis. There is another report of a case seen by Atkinson and Ivy.¹¹³ In this forty-seven-year-old woman, an edema of the feet and legs had regularly recurred since menarche at the age of thirteen. The pitting swelling started one week before flow and disappeared within a week after its cessation. At the time of the report, this condition had been prevented for one year by the administration of emmenin, after theelin had proved ineffective.

Among the many physiologic and biochemic, outside of mental and emotional, changes occurring in women in connection with the menstrual cycle, in the belief of Sweeney,¹¹⁴ too little attention has been paid to recurring edema. Patients often complain of tight and stuffy sensations felt in the abdomen, hands, or feet just before or during the menstrual flow. More careful observation will show pitting and often rapid increase in weight which may amount to several pounds. Controlling the weight of 42 healthy young nurses, Sweeney found that approximately 30 per cent of them showed a gain of 3 or more pounds usually just before the flow. Some showed true pitting edema. In his opinion, this phenomenon is more likely due to changes in the endocrine and sympathetic nervous systems than to temporary renal insufficiency or changes in blood constituents. Marked weight changes in connection

Exhaustive investigations undertaken by Bloech and Bergel¹⁰⁴ tend to reaffirm the widely accepted view of a definite influence of periodic changes in ovarian activity on the *carbohydrate metabolism*. They observed that in regularly menstruating women during the premenstrual and menstrual stages the outcome of a dextrose tolerance test is different from that made during the interval. When done near flow time, the test shows an exaggerated hyperglycemia with earlier maximum, a marked subsequent hypoglycemic phase, and occasionally a second peak. This is not the result of menstrual impairment of the hepatic parenchyma or of abnormal resorptive conditions in the gastrointestinal tract but is the manifestation of an increased irritability of the autonomic nervous system. This deviation is most marked in women with a sympathetic dysrhythmia in whom an alimentary glycosuria often appears during the menstrual flow.

Later in this review we shall speak of a glucose fermentation inhibiting substance in the blood described by Mommsen and Thyssen.¹⁰⁵

Also galactose tolerance tests show an increased assimilation during the premenstrual and menstrual periods as manifestation of alterations in neurosympathetic and hormone systems. In this connection, the fact may be mentioned that identical observations and conclusions have been mentioned by Ehrenfest¹⁰⁶ in a paper published in 1924. In it, it was pointed out that on women still in the childbearing period of life sugar tolerance tests should be made in the intermenstruum.

Since this premenstrual speeding up of the carbohydrate metabolism immediately increases with the start of a pregnancy (for this reason having been used as a pregnancy test), the phenomenon strongly supports the conception that premenstrual local and general systemic changes represent consistent preparation for the demands made by the implanted ovum for adequate nutrition. This point is emphasized by Muehlboeck⁴ in a review of more than 100 papers, dealing with changes in the various metabolisms during the menstrual cycle. He also states that changes in *basal metabolism* are dependent on so many external factors that it becomes impossible to determine exactly the significance of a particular phase of the cycle on such changes. In his opinion, there are no really reliable methods available for studying the *fat metabolism*, and reported findings in regard to varying levels of cholesterol in the blood in relation to the menstrual cycle are contradictory. All such studies should be done by means of long-continued observation of the same individual, since mere comparison of data from several individuals, which is commonly done, of necessity is unreliable and valueless for conclusions in regard to the influence exerted by a particular phase of the cycle.

Guggisberg,¹⁰⁷ in a study on female rats, found that their basal metabolism does not change with the phases of the estrus cycle and remains unchanged either after castration or after injection of relatively large doses (10,000 M. U.) of follicular hormone. Also in women with definite ovarian deficiency, he claims, normal basal metabolic rates can be found which are uninfluenced by administration of ovarian hormones. He concludes that ovarian activity plays no rôle in basal metabolism and could influence the latter only indirectly by way of the thyroid.

Interesting observations on the influence of the menstrual cycle on *Na Cl crystallization* in blood serum have been described by Bergauer, Bouček and Podrouzek.¹⁰⁸ A drop of blood serum is diluted with normal

ulatory conditions in the skin due to increased irritability of the vasomotor system, though physical and chemical factors acting on the skin may play a rôle. Both endogenic and exogenic factors, in his opinion, may be of importance in the etiology of the so-called menstrual dermatoses.

Garassi¹²⁵ and also Guthmann and Nagel¹²⁶ confirm the previously reported findings of Dietrich and Ellinger, that the *skin sensitiveness to ultraviolet rays* varies in the different phases of the menstrual cycle. In the week before, and on the first day of, the flow in about one-half of their patients, the resulting erythema became unusually intense, a fact worth considering when using ultraviolet radiation for therapeutic purposes. Guthmann and Nagel suggest that this change in sensitivity is connected with alteration in cation-ion relations of the blood through variations in calcium, potassium, and iron contents (see previous reference to a paper of Sehepetinsky⁹³).

We may in this connection mention a paper of Wright and Collip¹²⁷ on *nasosexual relationship*, manifested in the effect of estrogenic hormones on the nasal mucosa. Bresgen (in 1881) probably as the first observed a generalized congestion of the nasal mucosa during the menstrual flow, but to Mackenzie (1884) belongs credit for the first accurate description of this nasal phenomenon. The subject attracted more general attention through the work of Fliess (1897) who described the "genital spots" in the nose, and by means of applications to these spots successfully treated some cases of dysmenorrhea. Since then writers occasionally mention a special nasal type of dysmenorrhea. Since Seifert's exhaustive review of the literature on nasosexual relations (published in 1912), contributions have become scarce.

Wright and Collip reopen the interesting question by being able to show that in the female macaques the mucosa covering the conchae responds specifically to the administration of estrogenic hormones. They also ascertained that in the mature animal the conchal mucosae become hyperemic and swollen in a certain state of the sex cycle, exactly like the sex skin of the perineum. Similar investigations are now carried out on young nulliparous and pregnant women. It has become apparent that ovarian hormones exercise a specific, physiologic influence upon the mucous membrane of the conchae, both during the menstrual cycle in monkeys and during pregnancy in the human female.

D. Nervous System.—Exact investigations in regard to changes of *motor activity* of adult women in relation to the different phases of the menstrual cycle, seemingly for the first time, have been attempted by Billings.¹²⁸ Motor activity was measured by means of a pedometer and checked against simultaneous estrogen levels in the blood. Billings noticed a sudden and marked postmenstrual increase of activity which gradually regresses to a minimum before approach of the next period. He concludes that there seemingly exists a direct relation between motor activity and estrogen contents of the blood.

Observing most carefully six healthy young women in regard to variations in *mental ability and mental activity*, Hubert¹²⁹ was able to determine fluctuations but claims that they cannot be traced directly to particular phases of the menstrual cycle. Taking issue with Aschner,¹³⁰ Richter¹³¹ argues that any immediate causal relation between menstrual

with menstruation have also been recorded by Stewart.¹¹⁵ Curschmann¹¹⁶ discusses two cases of diffuse and transient climacteric edema.

C. *Other Skin Manifestations.*—*Herpes* in connection with menstrual flow is repeatedly mentioned in literature. Abraham¹¹⁷ describes a case of *intermenstrual herpes*. This woman, thirty-five years old, for the past two and one-half years had a vesicular eruption under the breasts which every month disappeared for about one week, namely from the day before onset of flow until about three days after its termination. Urbach and Kitamura¹¹⁸ report an instance of typical *neurodermatosis*. This particular type has been termed *dermatitis dysmenorrhoeica* by Pollard and Matzenauer, because they were able to establish its etiologic relation to an increased elimination of prolactin A and decreased appearance of follicular hormone in the urine. In this new case premenstrual aggravation was marked. She had been unsuccessfully treated for years with all forms of dermatologic therapy. The condition was improved, though only temporarily, by progynon.

Another form of menstrual dermatosis is an *erythema* on the lips and chin which, in a twenty-five-year-old patient of Fagioli,¹¹⁹ regularly disappeared with the onset of the flow. Peculiar *ulcerations of the vulva, vagina, or mouth* have been ascribed to anomalies of endocrine function. Wien and Perlstein¹²⁰ in a report of such a case offer a review of 29 similar nonvenereal ulcers collected from the literature. Kaufmann¹²¹ saw such vaginal ulcers in a woman thirty-three years old. Since they proved refractory to all therapeutic efforts and the patient was amenorrhoeic, he thought of the possibility of a hormonal disturbance. Treatment with ovarian hormones temporarily restored the menstrual function, and the ulcers became much smaller. With later return of the amenorrhoea, the ulcers again began to spread and repetition of injections of ovarian hormones once more was followed by reappearance of flow and complete cicatrization of all ulcerations. In a patient of Ziserman,¹²² ulcers in the mouth and occasionally on the vulva appeared periodically three days before the scanty flow for many years, and then persisted during the flow. During a pregnancy, the ulcers did not appear and this suggested the possibility of endocrine dysfunction as the etiologic factor. Ziserman, therefore, gave this patient 50 R.U. of anterior pituitary-like substance, subcutaneously, every other day. Prompt improvement was observed for three successive periods. Then this merely substitutive treatment was replaced by x-ray stimulation of the patient's pituitary gland. No ulcers appeared for the next four months, then there occurred one slight recurrence and none since. In the meantime, the menstrual flows had become regular and normal in quantity and duration.

Some time ago, by means of capillary microscopy, a premenstrual spastic state of skin capillaries has been ascertained. On the basis of this spasticity, Gebert¹²³ explains his own observation of a typical delay in *dermographic reaction* to skin irritation in premenstrual women. With approach of the time of expected flow, the reaction interval gradually becomes shorter, and the reaction becomes maximally prompt with onset of flow. Then the reaction time rapidly increases and with termination of bleeding again is approximately normal.

Freund¹²⁴ calls the attention of radiologists to the important fact that just before and during the flow the skin usually is more *sensitive to x-rays* than at other times. As explanation he suggests abnormal cir-

with general malaise and headache of the mother and great restlessness of the infant. They refer in this connection to the menotoxin question, of which more will be given later.

F. Gastrointestinal Tract.—Dyspeptic symptoms, such as anorexia, nausea, and vomiting, are frequently observed even in healthy women near or during the menstrual flow. They indicate a close relationship between gastric and genital functions, but according to Schlange,¹³⁷ the gastric disturbances are not, as often claimed, determined by changes in gastric acidity. In 25 women he found the variations in acidity before, during, and after bleeding to be very slight. A medical man studying gastric acidity in women needs not consider the menstrual phase.

Menstruation, in the belief of many women, affects their intestinal function. Halter and Pape¹³⁸ ascertained that among 481 normally menstruating women, 1.2 per cent claimed that they become constipated during the flow, and 9.1 per cent that defecations become more frequent. Among chronically constipated women, about 20 per cent asserted that at the time of the menstrual flow they have normal, spontaneous bowel movements.

Roentgenologic observations of intestinal motility made by Halter and Pape, with barium meals under continuation of the usual diet, led to the conclusion that menstruation influences intestinal peristalsis only in a small percentage of cases, and then more often in the sense of stimulation. Loeper, Lemaire, and Tanzin¹³⁹ used dogs in the endeavor to find the cause of such changes in gastrointestinal function. The experiments suggest that follicular hormone alone impedes the secretion of bile and reduces peristalsis of the gallbladder. Corpus luteum substance alone reduces intestinal peristalsis, but simultaneous administration of both hormones stimulates bile secretion. According to Molinengo¹⁴⁰ during the period of the flow, intestinal bacteria are more likely to enter into the blood stream.

G. Other Than Uterine Hemorrhages.—By way of introduction, it must be stated that periodic hemorrhages from various mucous membranes can be properly called *vicarious flows* only when true menstrual uterine hemorrhages are absent.

The appearance of minute subcutaneous hemorrhages, below the area at which a rubber bandage has been applied not too tightly for ten minutes on the upper arm, is well known as the *Rumpel-Leede phenomenon*. It is characteristic for certain infectious diseases (e.g. scarlatina) and for hemorrhagic diathesis. These petechial hemorrhages are due to an abnormal fragility of the endothelium of capillaries. Stephan (in 1920), presumably as the first, called attention to the fact that this test is likely to be positive in a perfectly healthy woman at the time of her menstrual flow. Other gynecologists (Schrader, Vogt, etc.) later confirmed this observation. Seydenhelm and Heinemann¹⁴¹ advanced definite evidence that this lowering of endothelial resistance is determined by a lowering of the estrogen contents of the circulating blood. More recently, Pistor¹⁴² discussed relations of the reticulo-endothelial system to the menstrual cycle. Testing the Rumpel-Leede (or as he calls it, the Seydenhelm) phenomenon on 205 healthy women, he found that the petechial hemorrhages almost without exception can be produced during the time of the menstrual flow, but rarely in the first

disturbances and depressive states is improbable in theory and remains unproved in practice, even though Aschner supports his theory by seemingly good therapeutic results.

Contrary to commonly held views, Peller,¹³² on a very large material, demonstrates statistically that attempts at *suicide* only in about 10 per cent of instances coincide with the last phase of the menstrual cycle, the highest incidence in this group, among young girls, falling on the first day of the flow.

In a most interesting manner, A. Mayer¹³³ discusses menstruation in its varied and complex *relations to life and health* of women. Most commonly flow time is one of retardation in the usual activities of life, very rarely a period of stimulation. The extent of this effect is greatly dependent upon the mental attitude of the woman. He feels that at the time of the menstrual flow all strenuous, competitive efforts better are avoided. There is no proof that criminal tendencies become more marked, though, in his opinion, the time of flow certainly is one of predilection for suicides. Preeocious menarche often impairs the future and particularly the mental development of the girl, and possibly reduces her survival chances, in part due to ovarian newgrowth and other pathologic conditions accounting for the precocity. As a rule, late menarche is associated with early menopause. Long-continued amenorrheas as the result merely of external influences, such as sudden fright or fear, are not rare. Dysmenorrhea often develops primarily on a neurotic basis, may represent a protest reaction, a fear reaction, an escape into disease in a milieu of dysharmonic family life, etc. He thinks that at the time of bleeding there is increased opportunity as well as susceptibility for infection, a point to which we shall return later.

E. Breasts.—Enlargement of the breasts, often associated with some tenderness just before and at onset of menstrual flow, is a common occurrence and is usually accepted as part of the assumed monthly preparation for a pregnancy.

Evans⁴⁰ thinks that cyclic changes in the breasts find their best explanation in a cyclic secretion of prolactine, a mammotropic hormone of the anterior pituitary gland. He feels that this stimulating effect cannot be ascribed to ovarian activity, because during pregnancy estrogenic substances actually depress prolactine secretion. Gabriellianz¹³⁴ emphasizes that excessive pain in the breasts usually is observed in association with some anomaly of the menstrual function. In his belief, it is due to an overproduction of corpus luteum hormones which leads to hyperplasia and increased desquamation of the epithelium of the milk ducts. In his detailed study of the relation of chronic mastitis to hormones, Taylor¹³⁵ states that the premenstrual hyperemia of the breasts is an obvious fact. The painful breast, in its simplest form, exhibits an exaggeration of these premenstrual vascular changes. In his opinion, no histologic proof has ever been furnished for the idea that swelling and pain could be due to a distention of the ducts with desquamated epithelial cells.

As will be shown later, this point is of some importance in regard to therapeutic administration of follicular hormones.

Temporary reduction of the diastase contents in the milk of lactating women during the period of menstrual flow is claimed by Steinert and Papp.¹³⁶ Very marked decrease of diastase often is found associated

was reported by Peters.¹⁴⁹ A twenty-five-year-old woman, since childhood suffering with severe migraine attacks always concurrent with menstrual bleeding, died suddenly at the time of onset of a regular flow. At autopsy there were found hemorrhages into all cerebral ventricles and aqueduct, but there were no pathologic lesions to account for them. Peters concludes that the only possible explanation could be intense vessel spasm incident to beginning of menstrual flow.

Hoff¹⁵⁰ very recently reported in detail observations made on six patients in whom *cerebral disturbances* occurred immediately before the expected period, leading to death in four of them. Autopsies in two patients showed diffuse hemorrhages in areas of the brain characterized by unusual proliferation of the glia. In two cases the clinical diagnosis of subarachnoidal hemorrhages seemed most acceptable. In one case, it seemed likely that there were syphilitic cerebral lesions. In the sixth case, a hemorrhage occurred from an aneurysm of the median meningeal artery. In five of the cases, a direct connection between the acute cerebral lesion and the menstrual function was strongly suggested by the fact that for some time before certain cerebral symptoms appeared only premenstrually, while at other phases of the cycle these women felt perfectly well. In four of the six patients, these symptoms previously had been diagnosed as migraine. Only in the instance of ruptured aneurysm could a direct connection to menstruation be doubted.

H. Postoperative Complications.—Popova¹⁵¹ warns against any long operations under general anesthesia during the time of flow. A statistical study of Hubert¹⁵² would indicate that postoperative complications are about of average frequency in women operated upon during the flow, but they appear in higher frequency when the operation is performed in the second half of the cycle and particularly in the premenstrual week. He suggests that this fact may be related to changes in the antibacterial faculty of the blood which at that time is lowered.

The common postoperative leucocytosis, Klein¹⁵³ asserts, is greatly protracted and does not disappear within the usual four or six days if the woman at time of operation was in the premenstrual stage. Not quite clear seems a discussion by Wheeler¹⁵⁴ of the effect of ovarian activity on wound healing. In a girl of seventeen years of age, the abdominal wound after a cholecystectomy and appendectomy failed to heal. There appeared in intervals a sanguineous discharge which "roughly coincided" with menstrual flows, though biopsy did not reveal endometrial tissue in the wound. Failure of all efforts to procure complete closure finally induced him to remove both ovaries (that is, he made another laparotomy!). This operation was followed by prompt and complete union. Wheeler refrains from offering any explanation for this seeming responsibility of ovarian function on the failure of healing.

According to the observations of Stetten,¹⁵⁵ it is almost certain that the postoperative course of even very ill patients will be smooth and uneventful, if after an abdominal operation the woman flows either at time or before the next expected period. (This really means that he either contradicts Hubert's aforementioned view concerning increased risks in premenstrual operations or that he removed in many of his patients the last corpus luteum.)

I. Various Diseases.—In general the relation between menstruation and disease is twofold. An existing disease may disturb normal men-

half of the eye. He suggests that the endothelial system is indirectly influenced by the ovarian hormones by way of alteration in blood cholesterol.

Kieser¹⁴³ emphasizes the relative frequency of *hemorrhages from nose, rectum, bladder, and even retina* accompanying or vicariously replacing uterine menstrual flows. Hemorrhages of this sort from the lungs, in his belief, possibly as a rule originate from unrecognized tuberculous lesions, and when observed in amenorrheic women do not represent then truly vicarious flows. He feels certain that in one of his patients, however, he succeeded in establishing the possibility of a *vicarious, non-tuberculous hemoptysis*. The details of this case are very interesting, but cannot be given here.

A paper of Paschke¹⁴⁴ deals with characteristic changes in the mouth in connection with the menstrual flow. Various parts of the *gingivae* become congested and swollen. They often bleed spontaneously and rather freely in connection with all dental manipulations or operations. This periodic hyperemia in some cases accounts for recurrent aphthous sores and labial herpes.

Predeseu-Rion¹⁴⁵ asserts that systematically repeated laryngoscopic examinations reveal in many young women a characteristic, premenstrual stasis, infiltrated swelling of the *pharynx and vocal cords*, accounting for burning sensations and a dry cough, occasionally causing slight admixture of blood to the sputum.

A hyperemia of the *urinary bladder* and especially of the trigone, as expression of the general, pelvic hyperemia, according to Saitz,¹⁴⁶ can be invariably found on cystoscopic examination made on the first day of the menstrual flow. Not so rarely small hemorrhagic spots or a small hematoma can be seen near the trigone, and for this reason at this time often erythrocytes will be discovered in the catheter urine. Naturally, this condition of the bladder mucosa will predispose the bladder to infection. There are cases known in literature of free hemorrhages from the bladder associated with the menstrual flow, occasionally also vicariously replacing the latter.

A most unusual case is reported, in a medicolegal journal, by Kuschelew.¹⁴⁷ A thirty-eight-year-old woman died suddenly just at the time of the expected menstrual flow. Autopsy showed that she had succumbed to a massive *intestinal hemorrhage*. Since no apparent cause for such a hemorrhage could be discovered, Kuschelew interprets this as a case of fatal, intestinal, vicarious menstruation.

Poos¹⁴⁸ states that the appearance of *eye diseases* of various kinds or their temporary aggravation in connection with menarche, and particularly the exact coincidence of such aggravation with the periods of flow, are well known in ophthalmic literature. In this latter connection, many observations have been recorded in connection with functional eye disturbances or such inflammatory conditions as blepharitis, conjunctivitis, phlyctenular eruptions, keratitis, scleritis, uveitis, optic neuritis, also hemorrhages in eyelids, conjunctiva, anterior chamber, glass body, retina, and orbita. In 1920, Groenouw published a comprehensive survey of this entire literature. Poos reports 2 cases of bilateral, extensive conjunctival hemorrhages appearing always simultaneously with the menstrual flows, ascribed by him to changes in the vasomotor system.

Decidedly rarer are coincident *brain hemorrhages*. The following case, described as "fatal brain hemorrhage with menstrual migraine,"

Hubert¹⁶⁰ claims that this faculty is entirely absent in the intermenstruum and at its highest point during the flow, thus rendering the woman more resistant to infection. This explains the normal incidence of postoperative complications for operations performed during the flow period.¹⁵²

Diabetes is temporarily aggravated by the secretory phase according to studies made by Introna¹⁶¹ on 28 diabetic women. Experiments made by Consoli¹⁶² indicate that disturbed ovarian endocrine function in diabetic women should not be ascribed, as usually is done, to impaired general health but to the maintenance of high blood sugar levels which result in direct damage to the ovarian stroma. A close connection between blood sugar and ovaries, in his opinion, was established in another series of experiments. A persistent hypoglycemia maintained with administration of insulin resulted in complete cessation of ovulation. Somewhat different are the views of Bompiani.¹⁶³ In his belief, involutionary changes in the genitalia and amenorrhea of diabetic women are the result of alterations in the anterior lobe of the hypophysis and of hypothalamic nuclei which control sugar metabolism. For this reason in some cases amenorrhea actually precedes the appearance of the typical signs of diabetes. In this manner also is explained the value of insulin in reestablishing the regular menstrual cycle and of fecundity in amenorrheic diabetic patients.

Some new facts have been developed in regard to the relation of *tuberculosis* to menstruation.

Under normal conditions a premenstrual rise of temperature is not unusual but always slight. Any marked elevation, therefore, in the opinion of Irma Jacoby¹⁶⁴ must be assumed to indicate a coincident pathologic process somewhere in the body. Febrile patients almost always will show a further rise of temperature just before the flow. That this holds true particularly for tuberculous women is emphasized by Jameson¹⁶⁵ who carefully studied 200 patients. Hemoptyses are prone to occur at this time, and Jameson feels that investigations should be made to determine whether pulmonary hemorrhages at this phase of the cycle might not be etiologically connected with coincident increased capillary permeability, a phenomenon we have already mentioned. In the opinion of Nobécourt and Briskas¹⁶⁶ both primary and secondary amenorrhea are common in tuberculous women and are dependent upon the severity of the process, even if it is not situated in the lungs. When in these patients ovarian function ceases, usually the tuberculous condition begins to improve.

Smilovits¹⁶⁷ interprets menstrual disorders in tuberculous women in terms of disturbances of the sympathetic nervous system due to tuberculous toxins. The menstrual disturbances in these patients, such as change in duration, amount and interval, and amenorrhea or dysmenorrhea are caused by degenerative processes in the ovarian parenchyma as the result of toxins. The always marked premenstrual fluctuation of temperature is the expression of hyperirritability of the temperature regulatory center. The pulmonary process is not necessarily influenced by the menstrual function.

Jameson¹⁶⁸ was interested in the question whether collapse therapy as well shows a favorable effect on concomitant menstrual disorders. Observations, made on 74 tuberculous women treated with thoracoplastic measures, showed that such interference does influence the menstrual

strual function and give rise to disorders, of which we shall speak later in detail. On the other hand, the marked somatic changes associated particularly with the premenstrual and secretory phases of the cycle can either favor the development of certain diseases, especially infections, or can alter the usual course of a coexisting disease. In this connection two facts of great practical significance have to be pointed out: (1) Patients suffering from almost any kind of disease or chronic discomfort are prone to state that the trouble is aggravated by "menstruation," by which, as a rule, is meant the menstrual flow. On more careful questioning, the physician usually can ascertain that this aggravation sometimes occurs during the week preceding the flow, sometimes during the flow, sometimes in the postmenstrual week and, at least occasionally, also in the intermenstruum. Such information, in part due to the loose manner in which the term menstruation is used, does not suggest any untoward effect of the premenstrual or flow phases but rather proves its absence. (2) When a patient definitely asserts that gastric disturbances, pain in the pelvis, breasts, or head, and other marked discomfort appears only immediately before or during the flow, such molimina can be considered as due to menstruation only when a careful examination has excluded the existence of any pathologic condition in any of these organs which might give trouble only at this phase of the cycle.

Diseases, resulting in general debility, are known to interfere with normal ovarian and menstrual function.

Kuramschina,¹⁵⁶ studying 72 women in a leper colony in Astrachan, shows that *leprosy* is prone to lead to late menarche, amenorrhea, and hypoplasia of the uterus. A secondary atrophy of the adrenals accounts for bronze color of the skin of lepers.

New statistics on the effect of *opium* have been supplied by Ko.¹⁵⁷ Of 100 female opium addicts, only a minority failed to show some harmful effect on genital function, usually manifested in scanty flows or premature menopause.

We will have to say more about menotoxins later in this review, but will mention here an article of Rugh¹⁵⁸ in which he describes acute attacks of *arthritis* in the knee and wrist, recurring regularly during the bleeding phase, in his opinion, probably having some relation to menotoxins.

The varying effects of diseases of most endocrine glands, and especially of the thyroid and pituitary, on menstruation are generally appreciated.

The temporary pelvic hyperemia, relieved with the start of the menstrual flow, satisfactorily explains increased discomfort or pain of pelvic inflammatory processes during the premenstrual week.

Schmidt and LaBaume¹⁵⁹ refer to the fact that in cases of gonorrheal infections it is customary to examine the vaginal secretions before or immediately after the menstrual flow, because increased secretory activity of the glands at these times is likely to bring hidden gonococci to the surface. On a large group of prostitutes under official control, they ascertained that the largest number of positive smears will be found when made between the third and fifth day of the flow. The practical importance of this observation is obvious, particularly because, as a matter of fact, such smears relatively rarely are made during the flow.

Reference already has been made to probable changes in the *bactericidal power of the circulating blood* in various phases of the cycle.

antuitrin-S (2 c.c. daily for ten days prior to flow) was followed by a sharp rise in the polymorphonuclear neutrophils on first day of flow in January, 1933. Two weeks later the patient caught "a severe cold in the head," which was followed by diarrhea. The neutrophils gradually diminished. She developed an abscess on the buttock and died in February, approximately at the time of the expected flow.

It seems a noteworthy fact that about 80 per cent of all reported cases of agranulocytic angina have occurred in females. That the question of etiology, however, is not yet settled can be seen from a report by Embleton.¹⁷⁴ He describes a case of rhythmical agranulocytosis in which the rise and fall in leucocytes did not stand in any relation to the menstrual periods "in contradistinction to the connection usually found in rhythmical cases." The extraordinarily regular rhythm in this case suggested to Embleton that it possibly expresses the life cycle of a parasite.

Sometime ago writers mentioned that strikingly often *scarlet fever* attacks will be found coincident with the menstrual flow. The idea thus developed that, like in instances of scarlatina during the puerperal state, uterine infections favored during the secretory phase of the cycle the causation of this disease. Already in 1926, Benjamin, however, had called attention to the fact that, as a rule, the eruption does not follow but precedes the beginning of the flow. Dienst and Neter¹⁷⁵ studied 219 cases of scarlatina in regularly menstruating women and found that in 55 (about 25 per cent) of them the eruption appeared during the period of the flow, which they considered to be entirely within the limits of probability. Thus they concluded that even this high incidence does not support the assumption of a causative endometrial wound infection. Bluemel¹⁷⁶ finds fault with their method of calculation. Figuring on a twenty-eight-day cycle and a four-day flow, only approximately 14 per cent of adult women are menstruating at a given time. Therefore Dienst and Neter, in the opinion of Bluemel, have proved an incidence higher than could be expected, but this higher incidence probably is due solely to the fact that the appearance of scarlet with its associated fever in a certain number of cases may hasten the appearance of the flow. A recent paper of Meminger-Lerchenthal¹⁷⁷ deals with the relation of fever to menstrual function. He refers to the well-known fact that sudden emotional traumas are prone to be followed immediately by menstruation-like flows which probably are anovulatory flows. It is possible that conditions are different with flows out of regular time, lately so often seen in women during influenza attacks, because a sudden rise of temperature may cause a premature ovulation. He emphasizes the often recorded observation that fever artificially produced for therapeutic purposes, e.g., by intravenous injection of typhoid vaccine, leads to premature appearance of the next expected menstrual flow. Efforts have been made to treat oligomenorrhea by means of artificial fever.

Benda, in 1925, described cyclic variations in cell permeability which affect the barrier between blood and spinal fluid. Jungblut and Engle¹⁷⁸ were interested in the possibility of such cyclic changes in this barrier playing a rôle in the development of a *poliomyelitis*. They found that blood serums of four young women, obtained either in intermenstrua or on the first day of the menstrual flow, actually varied in their ability of inactivating poliomyelitis virus in vitro. These experi-

function, sometimes proves beneficial, but often actually harmful. He thinks that a beneficial effect is chiefly dependent upon an improved general condition but warns that even when operation seemingly aggravates the menstrual anomaly, this does not signify a deterioration in the patient's general condition. Jameson (in contrast to Smilovits) doubts that menstrual disorders in these patients could be interpreted as manifestation of a toxemia. An article by Krieck¹⁶⁰ is entitled "Tuberculo-Toxic Symptoms During Menstruation" among which he includes elevation of temperature. When menstrual flows become profuse, return in shortened intervals, and are followed by amenorrhea, then, in his belief, the prognosis for the tuberculous process is unfavorable. The use of ovarian preparations for treatment of the menstrual disorder frequently aggravates the tuberculous lesion.

Studying 309 women suffering from pulmonary tuberculosis, Leeloux and Carez¹⁷⁰ observed that flow time to these patients often means a period of critical incidents, particularly if the disease is in a state of active evolution. They mention a fact which deserves emphasis in view of its great practical importance, namely that the common and serious accidents inherent to pneumothorax therapy are more prone to occur when the operation is performed during a menstrual flow.

We have previously discussed alterations of blood constitution and stated that we shall have later to say more about the question of *leucocytosis*. Frequently the statement is made that the number of leucocytes increases characteristically in the premenstrual week. This is denied by some investigators. Stephens and Lawrence¹⁷¹ studied six women during two cycles and failed to notice any particular changes in white cell counts. On the other hand, they had occasion to observe an instance of *agranulocytic angina* with recurrences at the time of menstrual flows. After bilateral ovariectomy no further attacks occurred. This patient at times took amidopyrin, and thus the etiologic cause of the recurrences is not absolutely clear. More suggestive of a connection between cyclic ovarian activity and this disease are the observations of Thompson.¹⁷² Out of 18 women in whom an agranulocytic angina was diagnosed, in 17 the subjective symptoms of the disease manifested themselves within one or two days from the onset of a regular menstrual flow. Six of these patients were observed in subsequent recurrences and in each of them each recurrence came coincident with a menstrual flow. The likelihood of a direct relation between ovarian hormones and this form of angina is further supported by an interesting observation made on a man who had cyclically recurring attacks of neutropenia always associated with marked changes of follicular hormone contents in the urine. A similar case, recorded by Jackson and Merrill,⁹¹ deserves detailed quotation. A woman, thirty years old, was known to have had four typical attacks of agranulocytic angina within the two preceding years. At onset of her fifth attack (end of 1931), she was flowing at expected time, and on questioning asserted that also the four earlier attacks had begun on the first day of a regular menstrual period. During 1932, she was carefully observed, and it was found that with the onset of each flow the number of polymorphonuclear neutrophils fell precipitantly, only to rise again rather rapidly to approximately the normal level (previously reported by Jackson¹⁷³). She felt well but in October, 1932, she had another attack. The typical premenstrual drop of neutrophils continued. Administration of

their habitual strenuous exercising often is finally followed by scantier and more painful flows. Kuestner furthermore claims that an excess of sunlight may lead to harmful effects of overexposure to ultraviolet rays on endocrine activity.

Nizza,¹⁸⁶ after an investigation made on Italian girls, warns against too great activity in athletics, though a moderate amount of exercise undoubtedly proves beneficial. Okamoto¹⁸⁷ deals with a different aspect of the problem. Menstrual flow at the time of the contest, especially in swimming, admittedly is disadvantageous, therefore, it seems desirable to delay the next flow if likely to coincide with the match. In this attempt, he was successful in about half of 29 girls by administering (orally) 1,200 to 2,500 M.U. of follicular hormone, daily for seven days preceding the expected flow. The delayed flow was normal in amount. He thinks that in some of these girls the hormone treatment actually improved athletic capabilities during the contest. Omura,¹⁸⁸ who also considers exaggerated sport activity of Japanese girls during the flow as likely harmful, mentions the curious observation that occasionally a girl during the flow will attain higher scores than while not flowing.

Secher¹⁸⁹ insists on exclusion of all pelvic disorders before a girl could be permitted to indulge in strenuous exercise. Outside of exceptional cases moderate athletic activity is free of all harm to the menstrual function.

Probably the most careful investigations along these lines have recently been reported by Skerlj.¹⁹⁰ In this exhaustive statistical study on 152 girls, first of all the periodicity of the flows had to be determined. As others before him, he found wide individual variations in length of cycles, and in duration and amounts of bleeding. As the result of strenuous exercise, consisting chiefly in skiing, approximately 80 per cent showed at least a temporary effect on menstruation, which in 50 per cent became permanent. In this latter group, about one-half showed lengthening of the intervals with increase of duration of flows. The writer emphasizes that these findings obviously are not generally applicable. A fairly common increase, e.g., of menstrual discomfort, might stand in connection with swimming in cold water. Such swimming, as well as sprinting, high jumping, weight lifting, etc., should be avoided during the time of the flow.

Vogt¹⁹¹ thinks that women accustomed to athletic sports can safely continue their usual exercises during the flow, though their muscular strength apparently is somewhat impaired at the time. All exertion must be avoided if the flows are free. Barbara Wittich¹⁹² studied 238 girls participating in a sport festival. In 82 per cent no noteworthy change in menstrual function had been noticed by them since taking up their respective sport. In the rest of them, some observed beneficial but others harmful effect. Apparently one-half of the entire group continued their athletic activities also during the period of the menstrual flow. Like Okamoto¹⁸⁷ also Zondek⁵ states that 100,000 to 200,000 M.U. of follicle hormone injected within the course of one cycle can delay or even prevent appearance of the next flow.

In concluding this chapter on menstrual hygiene, we may call attention to not uncommon irritation or even inflammation of the vulva from the use of modern cellulose pads. Cormia,¹⁹³ e.g., reported such a case of "contact dermatitis from Kotex pads." The cause may be solely mechanical though at times an allergic sensitiveness strongly suggests

ments, however, proved inconclusive in regard to barrier importance, because blood serum of the same individual apparently can change appreciably within a very short time in this effect on the virus.

IX. MENSTRUATION AND EXERCISE

Growing belief in the value of physical exercise and probably the approach of the last Olympic games, in which female participants played a significant part, plausibly account for the large number of contributions from all over the world, dealing with the influence of exercise on the menstrual function. In general, there seems agreement that moderate exercise is definitely beneficial to the healthy girl. Some of the opinions expressed in this connection seem worthy of special mention. Before quoting them, in alphabetical order of the authors' names, we shall refer to two German papers which consider the broader aspects of the effects of normal or abnormal ovarian activity on woman's health.

Wagner,¹⁷⁹ in accord with prevailing opinion in Germany, stresses the fact that woman can fulfill her great responsibility in the nationally important problem of propagation only if her genital apparatus is functioning normally, and this is dependent upon normal and rhythmic ovarian activity. He emphasizes the necessity of proper hygienic-dietetic care at the time of menarche to further a normal development, and later of prophylactic protection against the possible harm done by tobacco, morphine, cocaine, etc., or by overexertion or certain injurious occupations.

Discussing the influence of exercise on woman's health and of menstruation on her life in health and disease, A. Meyer^{133, 180} states that the usual effect of the flow is a slowing up, that menstruation is a somato-psychic problem with disorders caused solely by psychic factors. Therefore, the mental strain associated with maximal effort demanded by a competitive match may cause sudden cessation of a menstrual flow often followed later by profuse flows.

Allee Clow,¹⁸¹ among 2,300 girls interrogated in schools and colleges, encountered only 6 who asserted that they did not like to participate in games while flowing, but in no instance was an ill effect noted. Augusta Hoffmann¹⁸² made comparisons between two groups of girls, the one comprising young women working in various professions, the other consisting of women in vigorous training to become teachers of athletics. In this latter group, during the earlier periods of training, the incidence of menstrual anomalies of all kinds was decidedly lower than in the first mentioned group. In the further course of strenuous exercise of the second group, the percentage of menstrual disorders increased slightly, but, as Hoffmann feels, this not necessarily proves overexertion as the sole cause.

In Japanese girls, in the opinion of Iwata,¹⁸³ sport activity is likely to do harm and but rarely proves beneficial. He found that in Japanese girls, devoted to athletics, less than 50 per cent have normal and regular menstrual flows, a figure far below that for Japanese nonathletic and German athletic girls. Klotz¹⁸⁴ warns against violent activity, and especially against the strain involved in contests during flow time, because it inevitably exaggerates the physiologic pelvic hyperemia. Swimming at that time adds the risk of sudden chilling. Kuestner¹⁸⁵ claims that overexertion in the growing girl fosters abnormal pelvic development. An inquiry among teachers of physical culture revealed that

vaginal hemorrhage, an unfavorable effect of breast milk on the baby can be observed in intervals of approximately three to four weeks. We shall later return to this particular statement.

Recurrent attacks of arthritis during menstrual flows have been ascribed by Ruth¹⁵⁸ to the menotoxin discovered by Maecht. Repeating the experiments of Maecht and Lubin in regard to growth impeding effect of a menstrual hematotoxin on lupine seedlings, Mandelstamm, Tschaikowsky, and Boudarenko¹⁹⁸ raise the important point that this effect could be due not alone to variations in the lipoid but as well in the folliculin contents of the blood.

An analysis of newer literature on a possible influence of allergic factors on the menstrual function is rendered somewhat difficult by the indifference of some writers to indicate whether by "menstrual blood toxins" they are referring to toxins in the circulating blood at the time of the menstrual flow, or to toxins in the discharged menstrual blood. The term "menotoxin" more generally applies to toxic substances in the circulating blood. Ploss and Bartels emphasize that in all the so-called "superstitious" beliefs the bloody discharge itself plays the more important rôle. However, in the question of an assumed allergic etiology of certain skin manifestations, of general symptoms and of anomalies of the flow, including its abnormal painfulness, a clear differentiation between circulating and menstrual blood becomes essential.

Dogliotti¹⁹⁹ doubts the existence of a menotoxin because, in his experiments, human menstrual blood failed to show any effect, e.g., on the function of the isolated frog heart, on the blood pressure in dogs or on the neuromuscular system of frogs. The only positive reaction obtained consisted in a seeming lowering of the metabolic rate in rats fed on menstrual blood. Repeating the experiments of Maecht, but using discharged menstrual blood, he failed to notice any growth impeding effect on lupine seedlings.

Fleckner,²⁰⁰ investigating the effect of menstrual blood on plant growth, ascertained that with mere change of technique either retardation or stimulation of growth could be obtained. Thus menstrual blood might retard the development of a plant in a test tube but will markedly stimulate growth of the same plant growing in earth. He considers as untenable Schiek's idea of a specific menotoxin or Saek's assumption of a specific growth hormone. Saek²⁰¹ discussing the menotoxin literature stresses the fact that recognized botanists have expressed doubt in the conclusiveness of experiments in regard to plant growth retardation by menstrual blood. Growth stimulation as well has been observed, and this effect may be due to follicular hormones or other auxins present in the blood. He feels that this entire question is still far from decided.

One can only agree with this last statement when reading a recent paper of Mommsen and Thyssen.¹⁰⁵ They find that a substance which inhibits the fermentation of glucose is at times present in the *circulating blood* of healthy women. Its concentration gradually increases premenstrually and reaches its maximum just before onset of flow. During the flow this inhibiting factor diminishes and has disappeared in the intermenstrum. Examining the *discharged menstrual blood*, they find that this same substance is present in it in higher concentration (than in circulating blood) with its maximum level on the first day of

itself. In practice, we have found it both useful and convenient to instruct patients with vulva irritation during or after menstrual flows to place a few layers of fine tissue paper (on the market under various names) on the surface of the cellulose pad to prevent its immediate contact with the skin. It seems likely that the small rolls of cotton or cellulose, more recently marketed for introduction into the vagina during the flow, will cause vaginal irritation if not frequently replaced. Such tampons obviously should not be used by girls with an intact hymen, often cannot be used by parous women with relaxed vaginal walls, but are of definite advantage to professional dancers.

X. MENOTOXIN AND ALLERGY

Old and new experimental studies on supposed menstrual toxins have been exhaustively discussed by Macht and Davis.¹⁹⁴ "There is a popular belief among all peoples and all races, ancient, medieval and modern, that a woman at the time of her menstruation is unclean." The term unclean in this connection refers not merely in its literal sense to her flow but in a transitive sense implies a defiling and contaminating action. "Such a person is popularly believed to spread poison and to contaminate persons and objects with which she comes in contact." Even today, in France, women are not allowed to work during their menstrual period in the great perfumery manufacturing centers or to tend to silkworms.

In the first volume of *Woman* by Ploss and Bartels,¹⁹⁵ we find a special chapter, entitled "Popular Superstitions and Menstruation."

Popoviciu¹⁹⁶ describes the many taboos prevailing in Roumania and recites some personal observations. Bela Schiek, in 1920, reported comparative studies on withering of fresh cut flowers held by his nurse, during intermenstruum or at flow time, either with or without rubber gloves on her hands. Popoviciu duplicated these experiments with wild cyclamons. When touched by a menstruating woman, they withered promptly without any exception.

Scientifically arranged investigations in regard to this interesting phenomenon, generally considered a mere superstition, are limited in number. Approximately at the time of Schiek's report, plant physiologists had begun to emphasize the value of plants for experimental studies of the physiologic effects of drugs and other chemicals. In 1924, Macht showed that blood serum, blood corpuscles, saliva, sweat and other secretions (including breast milk) of women at the time of the menstrual flow contain a toxic substance that is characterized by specific pharmacologic and chemical reactions. This "menotoxin," in his opinion, can be found in all menstruating women, though in greatly varying amounts, but in each individual in maximal amounts just before or at the start of the flow. Macht and Davis¹⁹⁴ confirm their previous conclusions that menotoxin stands in close relation to oxycholesterol. Popoviciu ascribes the withering effects on flowers to cholin and creatin on the skin surface of the hands which paralyze the growth ferments of plants. According to Steinert and Papp,¹³⁶ as already mentioned, this menotoxin reduces the diastase contents of the milk in lactating women. Mommsen,¹⁹⁷ a strong believer in the existence of a menstrual toxin in the blood, considers the term "menotoxin" misleading. It is, in his belief, a substance, whose chemical nature is unknown but which probably originates in the lipid metabolism. Even if lactating women, he states, do not show any visible evidence of menstruation in form of a

directly the presence of a factor responsible for the allergic symptoms either in the menstrual discharge or in the circulating blood. Harrison²⁰⁶ saw a girl, twenty-three years old, who developed a giant urticaria with her menstrual flows. She was found to be sensitive to egg white. Elimination of eggs from her diet relieved her from the hives. Very gradually later eggs were added to her food and with onset of the next flow, the urticaria again appeared. Now a test was made with a diluted solution of a small amount of blood taken from one of her menstrual pads. An intraeuteaneous injection resulted in an attack of hives. She now was gradually desensitized against her menstrual blood, and at the time of the report she had had three successive menstrual flows without urticaria. This patient was found non-sensitive to her own blood serum or that of any other person. Harrison concludes that this girl presumably is sensitive solely to some factor in her menstrual discharge which acts as an allergen.

This same question is exhaustively discussed in a paper of Salén²⁰⁷ published only a little later than that of Harrison. His own investigations make it seem probable that the physiologic, cyclic variations in ovarian activity influence an existing allergy or allergic sensitivity. He quotes histories of patients in whom most severe attacks of asthma always coincided with onset of the menstrual flow. Also he prepared watery solutions of menstrual blood, which in every one of these patients yielded a strong skin reaction. Subeuteaneous injection of a dilution of menstrual blood extract, administered during the intermenstruum, in one patient reproduced the typical allergic picture she always offers during the menstrual period. Thus also Salén has furnished proof for the possibility of truly endogenic allergy.

Another important contribution to this complex problem has been made by Geber.²⁰⁸ It is known that in otherwise perfectly normal women, in connection with the menstrual flow, peculiar exanthemas appear. They are of various types, at times only minute papules near hair follicles, or more or less marked herpes eruption, localized or diffuse erythemas, urticaria, or pemphigus-like eruptions. Characteristic for all of them is that they are inflammatory lesions always appearing with the flow and disappearing after its cessation. Often they are associated with general symptoms, headache, indigestion, vomiting, joint pain, etc. In some instances these latter symptoms appear alone, without visible skin manifestations. All these symptoms express hypersensitiveness against certain substances entering the blood stream. Blood serum taken from such an individual during the time of flow and later injected during an intermenstruum will cause an urticaria. Blood serum obtained during an intermenstruum and reinjected during the next intermenstruum fails to exhibit any effect. Blood serum of a sensitive patient taken during the flow does not cause an urticaria in another woman; the menstrual allergen is specific. Geber feels certain that we are dealing with an allergic condition because previously (in collaboration with Rajka) he had shown that in a case of herpes menstrualis the Prausnitz-Kuestner test was positive.

The possibility of cures by desensitization naturally suggested itself. Assuming that at the time of the flow, when the symptoms seemed to be severe, the antigen would be at its maximum level, Geber experimented with blood serum obtained at that time. He tried this therapy on 26 patients, of whom 14 had symptoms of particular severity. At times

the flow. This fermentation inhibiting ability of circulating blood is different in different women and always varies in the same woman at different phases of the cycle. The phenomenon disappears after the menopause. Incidentally these writers mention that follicular hormone, thyroxin, and guanidin stimulate dextrose fermentation while cholin and acetylcholin in this respect are ineffective.

In part as the result of inaccuracies in terminology, already pointed out, but as well for other reasons, it is difficult to present clearly the views expressed in recent literature in regard to an assumed or established relation of toxins in the circulating blood or in the menstrual blood to allergic phenomena and certain anomalies of the menstrual function, especially to dysmenorrhea—to be considered in detail later.

Duke, in 1923, possibly as the first, expressed the opinion that a considerable number of patients suffering from various food allergies also complain of painful and frequent menstrual flows. Other writers, among them Eyermann (in 1927), Rowe (in 1928), Cooke, Kahn (in 1928), Robinson (in 1929), confirmed the possible etiologic relation of these conditions. In 1931, D. R. Smith²⁰² reported the histories of 12 allergic patients suffering from dysmenorrhea and concluded that his own observations lend strong support to the contention of Duke in regard to an influence of allergy on the menstrual function. Rowe²⁰³ claims that such uterine allergic reactions, consisting in painful, excessive, scanty, or irregular menstrual flows, may be limited strictly to this particular localization, and thus can occur also in women without any personal or family history of allergy. In his experience, the usual allergic reactions of an individual are either precipitated or intensified by a menstrual flow, possibly as a result of an increase in the basic metabolic rate. He doubts that the menstrual flow by itself can be the direct cause of the allergic phenomena, because elimination of the responsible food factor will prevent recurrence of all previous symptoms also during subsequent menstrual flows. Rowe stresses the necessity of careful allergic testing before any surgical or other major procedure is decided upon to relieve menstrual pain or excessive blood loss. It is noteworthy that Rowe here deals only with food allergy and fails to state whether test reactions are unusually marked or misleading in a woman near flow time. It seems desirable that investigations be made in this direction.

Dutta who previously (in 1928) had written on the striking coincidence of asthma and dysmenorrhea in the same woman, more recently²⁰⁴ described three cases of dysmenorrhea cured by desensitization to the particular pollen responsible for the asthma and asserted that in such patients the attacks can always be relieved with adrenalin.

An observation, recorded by Riebel,²⁰⁵ in his opinion, suggests that premenstrual allergic reactions may be due to hypersensitiveness to ovarian hormones. A twenty-nine-year-old, normally menstruating woman regularly developed on the day preceding the flow an acute erythema often associated with tachycardia. Skin test showed that she was sensitive to follicle hormone only during and for a few days after the regular flow. On repeated tests subcutaneous injections of folliculin soon after the period always caused the immediate appearance of the same erythema in intense form.

More significant in the problem of interrelations between menstruation and allergy are a few contributions which tend to establish more

ical picture necessarily is not definite since it is inevitably colored by the psychic and emotional state of the woman which, as we know, commonly during the flow phase is different from the usual state. In judging dysmenorrhea pain the physician unfortunately must depend to a large extent to statements made by the patient, and they are prone to be inaccurate and exaggerated.

A psychology study made by Thea Goldschmidt²¹⁰ led her to the conclusion that the disagreeable phenomena of menstruation are chiefly mental and traditional rather than biologic, and that "women are still under the spell of the primitive taboo." A. Mayer¹³³ restates the known fact that dysmenorrhea develops often on a neurotic basis and may represent solely a protest or fear reaction, an "escape into disease."

The gynecologist must realize that the seemingly common combination of dysmenorrhea and sterility does not necessarily indicate a causative relation between these two conditions, but in many instances is explained by the fact that a sterile patient is likely to overemphasize any, however slight, anomaly of her menstrual function, because in her own belief it plays a significant rôle in her inability to become pregnant.

Coexisting pathologic processes in the pelvis may become temporarily aggravated or more painful either as result of the premenstrual local hyperemia or on the basis of temporarily increased emotional sensitivity. It is essential to differentiate in each case such temporarily augmented discomfort or pain from that intrinsic pain which is directly dependent upon uterine changes due to menstrual activity. For the latter variously the terms primary, essential or intrinsic dysmenorrhea are used. Also "menorrhagia" has been suggested.²¹¹ The following terminology has been proposed by Medina:²¹² "algomenorrhea" for severe menstrual pain in the region of the small pelvis; "exmenorrhea" for exaggerated discomfort in any other part of the body; "dysmenorrhea" for a combination of both.

We must state that the term "dysmenorrhea" in this chapter is employed to designate specifically the intrinsic type.

The definite diagnosis of dysmenorrhea from this viewpoint requires careful clinical study of the patient, occasionally implying physical, biochemic, endocrinologic, and psychology examinations.

How difficult it may at times become to reveal the actual cause of such a pain is well illustrated in a case reported by Janson.²¹³ His patient had a seemingly characteristic dysmenorrheic pain at each flow. After long and futile study, the source of this pain was finally discovered in an x-ray picture: an incrustated sewing needle, deeply imbedded in the cervical wall, introduced many years before "to prevent impregnation."

Stone²¹⁴ estimates that about 35 per cent of all adult women suffer from some form of menstrual pain, among them primary dysmenorrhea being the most common type and the most difficult to treat successfully. Bell and Parsons²¹⁵ ascertained that of 840 women students entering the University of Michigan, 100 (12 per cent) complained of severe dysmenorrhea. Of these, 43 per cent showed a retroverted uterus, 9 per cent an abnormal ante flexion, while in 48 per cent, the uterus seemed normal in every respect. Twelve women were completely disabled at the time of flow and required opiates. In this last group, the uterus was retroflexed in 7, acutely ante flexed in 1, and normal in the remaining 4. In 3 instances fibromyomas, in 2 a chronic adnexitis was suspected, in

it was possible to secure satisfactory desensitization within one cycle, in some instances the first subsequent flow would cause less trouble; especially headache thus was relieved, but in most cases a cure could be obtained only with continuation of the treatment for two or three months. An occasional patient required later repetition of this treatment.

Not without interest in this connection is a paper by Perlstein and Matheson²⁰⁰ entitled "Allergy Due to Menotoxin of Pregnancy." A little girl, four and one-half years old, had for the last ten months severe attacks of bronchial asthma regularly on about the fourteenth day of each month. Complete cutaneous testing revealed the child to be sensitive to ragweed, house dust, spinach and other vegetables. Elimination of these substances failed to show any effect. No wheal formation followed intradermal injection of theelin, corpus luteum extract, posterior pituitary extract, or anterior pituitary-like urinary extract. Later, tests were made with leucorrheal vaginal discharge obtained from the mother on the last day of her menstrual flow, and it was found that only this discharge caused large reactive skin wheals on the child. It was then ascertained that the mother always menstruated in the middle of the month and on questioning the mother stated that previously, during the latter part of pregnancy and during the amenorrheic period of lactation of another infant borne in the meantime, she had noticed a freer leucorrheal discharge always about in the middle of each month. After the birth of this second child, the mother was accustomed to keep her first allergic child in her own bed. She was now instructed to keep this first child isolated from her during the entire time of her next menstrual flow, with the result that for the first time in eleven months this child missed her attack of asthma. The next month the child was again allowed to sleep with her mother and again she had a typical attack of bronchial asthma at the time when her mother was menstruating. This same experiment was repeated with the next two flows with the same result. Since then, the child has not been permitted to sleep in her mother's bed and has been entirely free of asthma. A few months later it was ascertained that the child apparently was not any longer sensitive to the leucorrheal discharge.

The observation as such undeniably is most interesting and proves the possibility of periodic allergic reactions of a child to the vaginal secretions of her mother. We doubt, however, the justification of identifying this maternal allergen, appearing in seemingly regular intervals during pregnancy and amenorrhea of lactation, as a "menotoxin." The writers base this deduction on Mommsen's already-quoted observation of periodic malaise in nurslings, which he ascribes to menotoxin present in spite of absence of a menstrual flow.

XI. DYSMENORRHEA

The profound anatomic, functional, and biochemic changes which, as discussed in a previous chapter, during her childbearing age periodically prepare the woman for a possible pregnancy, necessarily will give rise to a variety of subjective symptoms of which some express themselves in marked pelvic discomfort.

The term "dysmenorrhea" in the following paragraphs is employed in the limited sense of exaggeration of such discomfort to a degree at which it interferes with the individual's normal mode of life. Its clin-

effect of a therapeutic dilatation of the cervix is only temporary so far as this procedure loosens and softens the uterine wall by a reactive hyperemization. This effect, in his opinion, can more easily be obtained by diathermy or the administration of follicular hormone.

In a similar manner, a seemingly typical dysmenorrhea is produced by an internal uterine endometriosis through distention of endometrial glands which are lying deeper in an otherwise normal uterine wall. A dysmenorrheic pain as a result of compression of the engorged endometrium, therefore, will also appear in cases in which the uterine muscle is in a state of high tonicity due to increased irritability both of the muscle and of the vessels as the result of a disturbed thyroid-ovarian endocrine balance. For these cases, Fekete finds a mixture of papaverin, pyramidon, and luminal particularly useful.

Tedstrom and Wilson²²¹ observed that in every case in which a fasting blood sugar was found below 80 mg. per cent, the woman complained either of menstrual pain or nervousness, irritability or annoying weakness a few days before the flow. Increase of the carbohydrates in the food for about a week before expected flow yielded satisfactory results in about 80 per cent of the cases. Further tests with this same food régime showed that it relieves dysmenorrheic pain as well in women with normal blood sugar levels.

It proves rather difficult to harmonize this explanation of dysmenorrhea on the basis of a hypoglycemia with the equally enthusiastic report by Altsehul²²² of success in four patients with administration of insulin. Given subcutaneously with simultaneous intake of orange juice during the attack, the relief came almost immediately, all pain disappearing within thirty to sixty minutes. This author claims that different brands of commercial insulin seemingly vary in this particular effect on dysmenorrheic pain, some of them apparently being ineffective.

All recent discussions of either causation or treatment of essential dysmenorrhea are greatly influenced by newer information in regard to the respective parts played in normal menstrual function by different hormones supplied by various endocrine glands. Before analyzing these endocrinologic aspects of menstrual pain, it will be desirable to point out briefly certain facts outside of those already mentioned in a preceding chapter.

Experiments of Reynolds (1932) showed that the normal adult uterus of the rabbit (but not of the guinea pig, rat, or mouse) is usually in a rhythmic activity dependent upon estrogenic hormones supplied by the ovaries. Immediately after ovulation, the tone and activity of the uterus greatly decrease, the inhibition being due to the appearance of the corpus luteum hormone. According to Knaus,²⁹ the uterus of the human female behaves exactly in the same manner, though his claim in regard to the difference in the effect of pituitrin on the uterus when administered either before or after ovulation has been contradicted by many other investigators.

We find Witherspoon²²³ among the ardent supporters of the theory that primary dysmenorrhea is due to a deficiency in corpus luteum hormone (progestin). The pain is ascribed to strong uterine contractions, stimulated by the augmented output of estrogenic hormone during follicular ripening, which is not counteracted by a sufficient amount of progestin. The rational treatment of dysmenorrhea, therefore, would consist in supplying the missing inhibiting factor by either giving

4 enlarged ovaries were palpable. Treatment included attention to general and mental hygiene and special physical exercises. After eight months new tabulations showed remarkable improvement.

A similar survey was made by Ruby Cunningham²¹⁶ on over 14,000 female students of the University of California. About 50 per cent had some discomfort; in about 35 per cent the pain was severe. The dysmenorrheic girls in large numbers show a poor state of nutrition, poor posture, fallen arches, low blood pressure, etc. This same type of girls also often exhibits other disorders of menstrual function, such as deviations in intervals and duration of flow. Among them the incidence of amenorrhea, fluor albus, or menorrhagia is relatively higher. Only this latter feature, in the opinion of the writer, points to a possible relation of dysmenorrhea to endocrine disturbance which, however, in all probability is of relatively minor etiologic importance in comparison with the evident significance of constitutional deficiency.

Of interest is a contribution by Lakeman²¹⁷ because it represents a comparative study made on healthy girl students and girls employed in various industrial plants. The latter group showed a much higher percentage of severe complaints. The author, however, refuses to draw any definite conclusions, because she realizes that industrially employed women might possibly seize every available opportunity to absent themselves from work, or might be influenced by the less intelligent habit of assuming that girls during the menstrual flow are semi-invalids. Also Adams²¹⁸ and Miller²¹⁹ record the prevalence of bad posture among dysmenorrheic girls. They differ, however, in the interpretation of this fact. Adams, in 137 women, found 54 per cent complaining of menstrual pain. He feels that when none of the recognized etiologic factors for a painful flow can be discovered, faulty posture deserves consideration as a possible cause. Bad posture with marked lumbar lordosis and thoracic kyphosis, flattening of the abdomen, and enteroptosis probably results in venous congestion within the pelvic region, which can be improved by postural correction. Miller observed 302 college women consecutively for four years. He arrived at the conclusion that there does not exist any cause and effect relationship between bad posture and dysmenorrhea. Improvement in posture carries no assurance of any improvement of the coincident dysmenorrhea.

A discussion of dysmenorrhea obviously must refer to more or less severe pain appearing only during the time of the menstrual flow in cases of endometriosis. Extensive histologic studies have definitely shown that islands of seemingly normal endometrial tissue, wherever located, participate in the characteristic cyclic changes of endometrium. During the secretory phase, blood is discharged from the glands in the endometrioma, and if this blood cannot escape, typical, chocolate-colored hematomas form. Additional hemorrhages occurring monthly distend these cavities further and cause pain. Endometrial inclusions, chiefly when located in the uterus or the ovary, thus will lead to an attack of pain closely resembling that of a dysmenorrhea. Indeed this pain, recurring with each menstrual flow, is appreciated as valuable aid in the diagnosis of a suspected endometriosis.

Fekete²²⁰ emphasizes the fact that even in an uterus of the infantile type the menstrual pain is not due to a mechanical stenosis of the cervix but more likely to compression of the engorged endometrium within the rigid walls of the small uterus. Therefore, he reasons, the

"With the discovery of each new hormone," writes Heaney,²²⁶ "the literature is flooded with the tales of remarkable cures of dysfunctions of all sorts."

Clow¹⁸¹ finds little use for drugs in the treatment of essential dysmenorrhea and urges her patients to carry on their daily routines as regards diet, bathing, exercise, and work. Various special exercises (knee-chest position, hook-lying and curl positions) are considered particularly helpful by Bell and Parsons.²¹⁵

Fully in harmony with present-day interest of German physicians in naturopathy is Weiss's²²⁷ enthusiasm about hot mud applications to lower abdomen and back. He describes one case of prompt cure after previous futile treatment with diathermy, curettage, and organotherapy.

Boynton and Hartley²²⁸ secured complete relief in 33 out of 49 patients suffering from essential dysmenorrhea by giving them calcium glueonate alone or in combination with viosterol.

Stone,²¹⁴ who readily admits that the successful treatment of primary dysmenorrhea is a most difficult problem, asserts that in his hands the best results were obtained with cervical dilatation, gently done in the office with Hegar dilators during the latter half of the intermenstruum.

Adair²²⁹ took the opportunity of sounding a strong warning against the still used stem pessary, when reporting a case in which such a pessary had remained untouched in the cervical canal for fifteen years. In the subsequent discussion, Curtis mentioned instances of uterine perforation resulting from this appliance.

As already mentioned, Reynolds' theory of an antagonistic effect of folliculin and progestin, respectively, on the uterine muscle, in general, forms the basis for all the recent efforts to cure dysmenorrhea with certain endocrine substances. It would be impossible, if not superfluous, to attempt a review of this large literature, particularly because a part of it will have to be mentioned later in connection with the treatment of other disorders of menstruation.

Emil Novak, in a discussion of "Uses and Abuses of Gland Products in Gynecologic Disorders,"²³⁰ states that it seems probable that in some cases of primary dysmenorrhea the endocrinopathic factor is the important one, and then warns: "To give any ovarian preparation seems illogical because it is impossible even theoretically to figure how they could help, however, they might really aggravate the pain because scientific research has seemingly proved that estrin increases the contractility of the uterus."

Nevertheless, we find that Tunis²³¹ gave to his dysmenorrheic patients six injections of 1,000 M.U. each of menformon (folliculin), starting fourteen days after beginning of the last flow. He reports as his results: Out of 75 patients, 65 were cured and 8 improved. Kaufmann²³² in a recent paper says that encouraging results can be obtained in dysmenorrheic women with follicle hormone. We shall see later how such favorable effects have been explained.

Logically, of course, excessive uterine contractility could be relieved only by the administration of corpus luteum hormone.

It proves convenient to cite in this connection some of the literature dealing with this hormone.

Corpus luteum hormone in a pure state (known in two different crystalline forms) has been called "progestin" by Corner and Allen, and seemingly is identical with Hisaw's "corporin" and as well with

corpus luteum hormone or substituting for it the anterior pituitary-like extract from urine which contains the luteinizing principle.

A critical analysis of all "Modern Theories of Dysmenorrhea" is presented by Cannon.²²⁴ The characteristic dysmenorrheic pain, he states, is essentially spasmodic or tetanic in character, and it is generally agreed that all types of visceral pain are due to exaggerated muscular contractions. There is considerable evidence that follicular hormone stimulates, and corpus luteum hormone inhibits uterine contractility. Thus with some plausibility some endocrine imbalance, either a quantitative or a chronologic disturbance, has been postulated to account for dysmenorrhea. Whitehouse (in 1926) has claimed that any abnormal detachment of the menstrual decidua is invariably associated with pain. Cannon is willing to concede only that the decidual tissue appears to act as a foreign body provoking muscular contractions (a thought expressed by Ehrenfest in 1908). If irregular uterine contractions, Cannon continues his argument, were the cause and not the result of abnormal separation of the menstrual decidua, we would have a right to expect such abnormal separation in every case of dysmenorrhea. The marked decidual reaction in cases of membranaceous dysmenorrhea, indeed, appears to indicate an actual accentuation of the luteal phase, and thus Cannon arrives at the final conclusion that "we are justified to infer that a dysmenorrhea associated with endometrial fragments is fundamentally due to an overactivity of the corpus luteum hormone, which in turn is due to overactivity of the luteinizing hormone of the anterior pituitary body." This certainly impresses one as a strong argument against the reasonableness of the dysmenorrhea therapy recently advocated. Cannon feels certain that the etiology of dysmenorrheic pain cannot be reduced to a single cause.

In connection with Cannon's reference to dysmenorrhea membranacea, mention can be made here of a paper by Pohl.²²⁵ He describes a case in which he prescribed thyroid extract because thyroid hypofunction was marked. Discharge of menstrual membranes ceased promptly and, therefore, in 4 other cases he tried thyroid extract together with anterior pituitary-like hormones, and suggested that roentgenization of the hypophyseal gland should be added to obtain satisfactory results.

Reading the immense literature on dysmenorrhea, mostly extolling results with this or that therapy, one cannot fail to be impressed by the tendency of writers to fall into deceptive *post hoc ergo propter hoc* reasoning. Many writers appreciate the important rôle played by suggestion in the seeming efficacy of any therapeutic measure applied to a woman in a highly nervous and emotional state while suffering pain. The possibility of any suggestive influence in experimental therapeutic investigations, at times has been carefully avoided in various manners. But after all, even with heterosuggestion reduced to its possible minimum, a patient anxious to obtain relief, hoping to get it from whatever new form of therapy is applied, still remains under the strong influence of autosuggestion. Older physicians, familiar with the dysmenorrhea literature of the past, cannot help feeling skeptic about many of the excellent results claimed for newer procedures, and especially those obtained with endocrine preparations. Excellent results were as frequent then when, as we now know, these preparations actually contained none of the supposed hormones or only in minimal and surely ineffective quantities.

Into this same group of indirectly attempted correction of disturbed ovarian function, we must place the suggestion of Koschade²⁴⁰ to administer "anterior hypophyseal preparations" percutaneously by means of skin inunctions. He asserts that in this manner even the severest types of dysmenorrhea, which have proved refractory to all other known forms of therapy, have been permanently cured by him.

Less enthusiastic sound the conclusions of Meigs²⁴¹ who presents a clear and exhaustive discussion of "Female Sex Hormonology." Treatment of endocrine disturbances in the female, he states, is possible on an intelligent basis. A thorough understanding of the underlying principles of pathology and physiology of treatable endocrinopathies is essential. "Treatment of dysmenorrhea with hormones is unsatisfactory."

In a paper dealing chiefly with endocrine therapy of dysmenorrhea, Israel²⁴² emphasizes that no adequate explanation of this troublesome condition so far has been given. The importance of psychic trauma as an etiologic factor is often stressed and particularly by those who extoll the good effects of psychotherapy. Perhaps the most important rôle played by the psychic element in dysmenorrhea is that which complicates the proper evaluation of any therapeutic measure employed.

Discussing many contributions on this subject, Israel also refers to Reynolds' idea of a corpus luteum deficiency which is supported by Novak. He argues (almost like Cannon) that such a hormonal deficiency would have to express itself in a deficient formation of the endometrium. However, Mazer (in a personal communication) has informed him that the microscopic study of the menstrual endometrium of 20 women with typical dysmenorrhea showed in 14 instances a typical and normal progesterin phase. His own experience with organotherapy in dysmenorrhea proved disappointing: Gonadotropic substances from urine cured 1 out of 10 patients; the estrogenic principle given by mouth (emmenin, progynon) cured 1 out of 16 patients, and the estrogenic substance given hypodermatically cured none of 13 patients.

A neurogenic basis, according to Israel, has been advanced by some authors who ascribe the etiology of primary dysmenorrhea to an abnormal reactivity of the cervical nerves, leading to spasm of the circular musculature. On this basis, a form of neurosurgical therapy, namely resection of the superior hypogastric plexus (presacral nerve) has been evolved.

In regard to such operative treatment, a few interesting correlated facts must be mentioned. At about 1925, Cotte had suggested this operation for the relief of intractable pelvic pain (usually due to carcinoma) including dysmenorrhea. In 1929, Bloss reported 90 per cent of cures of such pain by means of injection of 70 per cent alcohol into the cervical ganglion. This same procedure recently has been applied by Alberta A. Davis²⁴³ who blocked the Lee-Frankenhauser plexus by means of 1 c.c. of 95 per cent alcohol injected under epivian anesthesia. She cured her 6 patients of dysmenorrhea but emphasizes that the procedure cannot be considered as free of danger.

According to the anatomic studies of Keiffer,²⁴⁴ the cervix represents a sphincter whose tonus is controlled by a reflex arc which runs through the lumbar cord and the cervical ganglion. Kennedy²⁴⁵ seemingly proved a trophic effect of estrogenic substance on the cervical ganglia and established degenerative changes in the Frankenhauser plexus fol-

the "luteosteron" of German investigators (Slotta, Fels, Rushig, etc.). In order to avoid confusion, it has been proposed to name this pure hormone "progesterone." In regard to this hormone, Corner¹⁰ states: "As yet no preparation suitable for clinical use has been put on the market. Several European manufacturers, however, are actually advertising the drug under various names, such as 'proluton,' 'luteogen,' 'lutex,' etc."

It seems important to point out these facts, because quite recently Campbell and Hisaw,²³³ speaking of corpus luteum treatment of dysmenorrhea, particularly emphasized that they used an extract, which they especially prepared from corpora lutea of animals in Hisaw's laboratory (a pure corporin free of the estrogenic principle) because "many biologic products have been marketed in the past as corpus luteum which have contained very little of this hormone, if any." Trial with pure corporin, in their selected 11 cases, showed that this substance can give temporary relief "but that nothing can be said yet about any permanent relief after discontinuation of the therapy."

In 17 instances of dysmenorrhea, Elden and Wilson²³⁴ saw complete relief in 8, partial relief in 2, and no relief in 7, using progesterone (Sehering). They explain good results on the basis of Schroeder's theory: Sufficient relaxation of the uterine musculature is obtained to insure adequate circulation thereby overcoming abnormally increased congestion. Busehbeck²³⁵ found administration of progynon B oleosum in the first half of the cycle followed by proluton in the second half, to be useful in the treatment of dysmenorrhea.

It is probably not sufficiently clear to many practitioners that most of the marketed preparations, suggesting by their names that they contain corpus luteum hormone, as a matter of fact contain solely the anterior pituitary-like, luteinizing factor extracted from the urine of pregnant women. This factor is expected to supply indirectly the supposedly deficient progesterin by stimulating the luteinization process in the ovaries of the patient. More will be said later on this point, but it must be pointed out here, that Witherspoon, and many others, were using only these anterior pituitary-like substances.

Of late among newer organotherapeutic preparations used by gynecologists often mention is made of emmenin. It is an extract made from placental tissue (Collip) which contains as its chief active principle a complex of theelol. Of 40 dysmenorrheic patients, treated with emmenin by Goldberg and Lissner,²³⁶ more than 60 per cent were relieved to a remarkable degree. Watson²³⁷ found results with this substance particularly gratifying if the pain was caused by severe uterine contractions.

Analyzing results secured with emmenin in various menstrual anomalies, in a series of 472 gynecologic patients, Campbell²³⁸ states that it showed no effect in primary amenorrhea and its best effect in dysmenorrhea when the treatment was continued through at least three consecutive menstrual cycles.

Also based on the idea of indirectly stimulating the formation of corpus luteum tissue is the administration of small doses of x-rays to the pituitary gland which is employed now in the treatment of various forms of disordered ovarian function. Mazer and Spitz²³⁹ observed that such radiation often relieved, completely and permanently, primary dysmenorrhea.

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lowing castration. Therefore, he is willing to attribute good therapeutic results reported after administration of estrogenic hormones in cases of primary dysmenorrhea to the ability of these hormones to restore atrophic ganglion cells to normal activity.

Cannon²⁴⁴ gives a detailed description of the influence of the abdominopelvic autonomic nervous system on the uterus. The pelvic visceral nerve, in general, acts as a detrusor or motor nerve on the uterus, bladder, rectum, and pelvic colon, and is the inhibitor on the corresponding sphincters. On the other hand, the presacral nerve is the inhibitor of these organs themselves. Therefore, dysmenorrhea associated with vesical and rectal disturbances is due to overactivity of the abdominopelvic sympathetic nerves. In his belief, Davis²⁴⁶ goes too far in applying this theory to all cases of dysmenorrhea.

Adson and Masson,²⁴⁷ as well as Keene,²⁴⁸ give the history of nerve resection and describe in detail the anatomy of the nervous plexus. Good results from presacral sympathectomy for dysmenorrhea are also reported by Bailey and Cannady,²⁴⁹ Counseller and Winchell,²⁵⁰ De Courey,²⁵¹ Sellers and Sanders,²⁵² Shaul,²⁵³ Wetherell,²⁵⁴ and others.

Special mention must be made of a paper of Bakscht.²⁵⁵ In two cases of intense and intractable dysmenorrhea, he finally felt forced to remove the superior hypogastric plexus. Careful histologic study of the excised tissue in one of the cases showed marked inflammatory changes in the nerves, suggesting the possibility that an inflammatory process in these nerves, in some cases, might represent the etiologic factor for the dysmenorrhea.

Statements made by the various authors in regard to sympathectomy can be briefly summarized as follows: Presacral sympathectomy for primary dysmenorrhea is the last and only choice after all other known therapeutic procedures have failed. In cases of secondary dysmenorrhea, the resection can be done incidentally to the operation primarily required by the pelvic pathology responsible for the pain. Occasionally this operation proves very difficult and hazardous. It is, however, always preferable to hysterectomy or bilateral ovariectomy, which in the past frequently has been, and still is, done in aggravated cases. Theoretically one should expect postoperative impairment of bladder and rectal function; as a matter of fact, catheterization is required for a short time only in some instances. Follow-up observations so far indicate that the operation does in no way affect menstrual function, parturition, fertility, or libido. It seems that it permanently relieves the menstrual pain. In experiments on rats, Schwartz and Buxton²⁵⁶ recently demonstrated that ovulation continues after complete severance of the ovary from the sympathetic nervous system.

This chapter on dysmenorrhea seems fittingly closed with a quotation of remarks made by Emil Novak in discussing the cited paper of Keene: "The psychic factor is such an ever present one in the evaluation of treatment in cases of dysmenorrhea, that one can not set it aside even in appraising the results of presacral sympathectomy. However, theoretically one must admit that it could work."

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Correspondence

August 13, 1937.

To the Editor:

Thank you for calling my attention to an error in a figure in my paper "The Treatment of Carcinoma of the Cervix by Wertheim's Operation" published in Volume 30.

On page 817 in the last paragraph the ten-year cure rate (reckoning as dead of carcinoma all patients lost sight of or dead of other disease) is wrongly calculated as 20 per cent whereas the figures I cite show that it actually is 29 per cent.

I must have missed the error when I read the proofs and shall be obliged if you will publish this correction.

VICTOR BONNEY.

149 Harley Street, W. 1
London, England.

Item

American Board of Obstetrics and Gynecology

The next examinations (written and review of case histories) for Group B candidates will be held in various cities of the United States and Canada on Saturday, November 6, 1937 and Saturday, February 5, 1938. Application for admission to these examinations must be filed on an official application form in the office of the Secretary at least sixty days prior to these dates.

The general oral, clinical, and pathological examinations for all candidates (Groups A and B) will be conducted by the entire Board, meeting in San Francisco, California, on June 13 and 14, 1938, immediately prior to the meeting of the American Medical Association.

Application for admission to Group A examinations must be on file in the Secretary's Office before April 1, 1938.

For further information and application blanks address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh (6), Pa.

Erratum

In the September, 1937 issue, page 439, the article "Experimental and Clinical Therapy of Vulvovaginal Mycosis" by H. Close Hesselstine—Table II should have been the first half of Table I instead of a separate table, thus making seven tables instead of eight. The text refers to table numbers as they should have appeared in print excepting the last, which was printed VIII instead of VII.

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(To be continued.)

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exercise and "strange and wonderful preparations." Both the Old Testament and the Talmud give detailed advice concerning the conduct of women in pregnancy. In India the Hindu priests held conclaves in which obstetric nurses were consecrated and instructed in the prenatal and postnatal care of their patients.

Hippocrates and his school centered attention largely on the prevention of abortion. They warned against excessive purgation and coitus. Fear and great excitement might also interfere with the proper development of the pregnancy.

More explicit than Hippocrates was Susruta, writing in India in the second century before Christ. He set forth rules as to food and drink, exercise and clothing. The pregnant woman should be surrounded by cheerful company both for her own and her child's sake. He cautions against marriage with a woman whose family is tainted with epilepsy or tuberculosis.

In the days of the Emperor Trajan lived Soranus of Ephesus who devoted many chapters of his book on gynecology to prenatal care. Concerning the tendency to abortion from physical exertion and trauma, he writes quaintly: "Houses built on a firm foundation stand unshaken a long time, whereas the house that has a bad and loose construction falls under the slightest strain." Wrinkling of the abdominal skin can be avoided by anointing with a wax ointment mixed with oil made of unripe olives and myrtle. Toward the end of pregnancy a warm sitz-bath softens the tissues and produces an easy labor.

In the succeeding centuries and through the middle ages attention was directed largely to the management of labor and no important contributions were made to the study of prenatal care.

In 1584 a French physician, Seevole de Saint-Marthe, wrote a Latin poem entitled "Pædotrophia" (the nurture of children), containing much good advice on prenatal care. It opens with the lines:

"Don't till 'tis born defer thy Pious care
Begin betime and for its birth prepare."

Further on it reads:

"Refresh thy weary limbs with sweet repose
And when fatigued thy heavy eyelids close,
Be careful how your meats you choose
And chosen well, with moderation use."

Not until we come to the great Mauriceau in 1668 do we again find a significant contribution to the hygiene of pregnancy. In his *Maladies des Femmes Grosses* he devotes an entire chapter to this subject, beginning: "The pregnant woman is like a ship upon a stormy sea full of white-caps, and the good pilot who is in charge must guide her with prudence if he is to avoid a shipwreck."

"Fresh air, avoidance of extreme heat or cold, and freedom from smoke and foul odors are essential to her health. She should eat well-cooked

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THE STORY OF PRENATAL CARE*

PRESIDENTIAL ADDRESS

FRED J. TAUSSIG, M.D., ST. LOUIS, MO.

BY PRECEDENT, the address of your presiding officer has been directed not to the presentation of some new scientific achievement but rather to the analysis of underlying movements or philosophies that influence our special field of medicine. Sampson spoke to you of "Hobbies," Gellhorn on "Constitutional Factors," Graves on "The Control of Life"; and gracefully worded historical reviews have been presented by Chipman, Keene, Anspach and Watson. Having in mind this year's symposium on the prevention of eclampsia, it seemed fitting and perhaps of some interest to narrate briefly the story of prenatal care.

THE STORY OF PRENATAL CARE

From the beginnings of time the pregnant woman has always been regarded with reverence. Special privileges were granted her and so sacred was her abode that even a murderer seeking shelter under her roof could not be taken forth and killed. If she was physically injured by some one, the punishment was death. If she herself had done some crime, verdict was postponed until her child was born.

Many ancient records contain instructions for the care of pregnant women. A Chinese work enjoins them to avoid rich food, excessive

*Read at the Sixty-Second Annual Meeting of the American Gynecological Society, Swampscott, Mass., May 31 to June 2, 1937.

NOTE: The Editor accepts no responsibility for the views and statements of authors as published in their "Original Communications."

walking." Ledesert warns against listening to the stories of gossips and matrons concerning the terrible experiences of other women in labor.

Venesection was accepted as a routine procedure during pregnancy among French obstetricians of this period. The problem was how often it should be done, at what period, from what extremity the blood should be taken and in what amount. It is interesting that at this same time German writers (Buseh, Boer, Jörg, Naegele) were almost a unit in pointing out the dangers of routine venesection. Their instructions for the care of pregnant women do not otherwise differ materially from those already described.

In England, Denman (1801) warns against partaking of animal food in pregnancy. Women at this period usually prefer vegetables, fruit, and everything cooling. Concerning purgation he writes: "The more gentle the means for the removal of costiveness, the more eligible they are, provided they answer the intention." He warns against the use of opiates for insomnia. A glass of cold water at bedtime will often suffice.

American obstetricians of the nineteenth century made a few valuable additions to prenatal care. W. Tyler Smith (1849) urges dental hygiene in pregnancy to prevent complications that may lead to abortion. Hodge stresses psychic management. The expectant mother should indulge in suitable reading and cheerful conversation, keeping away all stories relating to the complications of labor in other women.

Before considering present conditions among civilized peoples, a few examples of the customs among savage races might be of interest. Superstitions of all sorts are deep-rooted. Evil spirits are believed to be the cause of fetal death and abortion. Yawning is very dangerous, for the demon seizes this opportunity to jump into the body and kill the child. Beware of walking in the moonlight, as there are devils about! Pregnant women are sequestered in special houses away from harmful influences and in one tribe a bell is placed on the ankles of pregnant women so that the tinkling sound will warn others to keep away. In South America the natives do not eat lamb for fear of giving their child a stub nose. Salty or greasy food is declared harmful and a diet limited to cocoanut milk is advised in the last months.

Numberless examples are related of maternal impressions. In fact this subject has been ardently discussed pro and con all through the ages up to the present time. The Greeks and early Christians considered that beautiful children were the result of gazing at beautiful objects in pregnancy. From Utrecht comes a yarn related by Schwammerdam in 1672 of a woman who while pregnant saw a Moor, and to avoid having a black child quickly washed herself with warm water. The child at birth was white except between the toes and fingers, spots untouched by her ablutions. Birth marks were often produced because certain foods had been denied the pregnant woman. Against the views

wholesome food in small amounts at intervals rather than at one large meal. Forbidden are highly spiced pastries, for they create gas. Fresh fish caught in streams are better than lake fish. And with this food a bit of good old wine, tempered with water, rather red wine than white wine, aids the digestion. Beware of cold drinks, for did not the Empress of Austria in July, 1677, take strawberries and ice, and abort at the fourth month of her pregnancy?" Since the prominence of the abdomen in pregnancy prevents women from seeing their feet, Mauriceau advises low-heeled shoes which will prevent them from tripping. Stooping in the later months may lead to faulty position of the child and interfere with the somersault that normally brings the head into the pelvis. For constipation he recommends eating apples, stewed prunes, and fresh figs. If necessary, he prescribes a mild enema of marshmallow, pellitory and anise with two ounces of beet sugar and a little oil.

Above all Mauriceau harangues against those terrible whalebone corsets worn by women of the upper classes who wish to conceal to the last moment the fact of their pregnancy. Squeezed from above, the abdomen is distended below. "When the mother finds her abdominal walls wrinkled and pendulous like a bag," he writes, "the poor midwife is accused of not having used the proper ointment, when the real cause lay in the prolonged wearing of the corset." The age-old custom of bleeding pregnant women is accepted with reservations. Nevertheless he cites a case in which a woman was bled 90 times in one pregnancy without apparent harm.

From Mauriceau we jump to the beginning of the nineteenth century for other evidence of special interest in prenatal care. In preparing this paper I glanced through the Catalogue of the Surgeon General's Library and was amazed to find record of no less than 55 dissertations written by graduates of French universities from 1800 to 1840 on the "Hygiene of Pregnant Women." I contrived to read about twenty of these dissertations. As a whole they do not display any great originality, and the manner of treatment is rather stilted; but their number is certainly evidence that French obstetricians of that period were keenly alive to the importance of giving prenatal instructions to pregnant women. There is a good deal of common-sense advice in some of these dissertations and a few examples may be of interest. Leglay writes (1812): "Have indulgence for the pregnant woman's caprices, listen to her desires with complaisance, console her and in place of the severity of the doctor, adopt rather the affectionate tone of a friend or a father." "Walking is the best form of exercise," says Nolette, "but it should be done in moderation and not transformed into a task or it will lose its advantage. Rather should the path of her promenade have pleasant surroundings and be made with good friends whose conversation may have so much charm that she will forget what was the purpose of her

In Germany autopsy findings on eclamptic patients demonstrated the consistency of kidney pathology in these cases.

It was an accident of economic circumstances that led to the establishment by E. B. Sinclair and G. Johnston of the first prenatal clinic in the world at the Dublin Maternity Hospital in 1858. Owing to the crowded condition of the hospital, applicants for maternity care had to present themselves for admission several months before their expected confinement. Their card had to be signed by one of the physicians of the hospital, who took this occasion to make a brief record and physical examination. Every woman with edema, headache, dizziness, or albuminuria was treated actively. She was instructed to attend the dispensary regularly, and, if necessary, was admitted into the chronic patient's wards of the hospital. Here she was purged freely and repeatedly, made to maintain a horizontal position in a cool ward, and allowed none but the mildest and lightest nourishment. Sinclair and Johnston found that by these measures the incidence of eclampsia was greatly reduced. In fact almost the only patients with eclampsia were untreated emergencies who had not come to the dispensary.

The next important advance was the discovery of blood pressure elevation in eclampsia. It was a lapse of almost half a century from the first mercury manometer used by Ludwig in his animal experimentation, to the air-inflated sphygmomanometer of Potain in 1888. Working with the latter instrument Vinay in 1894 noted the regular occurrence of a high systolic blood pressure up to 180 to 200 mm. of mercury in women with eclampsia. Three years later Vaquez and Nobecourt amplified these findings and found that they preceded the convulsive seizures. At the German Gynecologic Congress at Giessen, in 1901, Ffith and Kroenig reported a uniformly high blood pressure in preeclamptic patients. In the same paper they also showed certain differences in the freezing point determinations of the maternal and fetal blood. In the discussion that followed, the question of freezing point was carefully considered but the value of their blood pressure findings was completely overlooked.

At Johns Hopkins University in 1903, H. W. Cook and J. B. Briggs made careful studies of blood pressure after operations, during normal pregnancy and in eclampsia. Their conclusions were: "It is especially with regard to the early recognition of the onset of eclamptic features in any case and the possibility of instituting prompt and vigorous treatment for their relief that systematic blood pressure records may be of value to the obstetrician. The onset of hypertension at any period of pregnancy should always excite the apprehension of eclampsia in the absence of other recognized causes of abnormally high blood pressure."

Although this paper was published in the Johns Hopkins Hospital Reports in 1903, neither it nor the preceding European reports were mentioned in the symposium on eclampsia held by our Society two years later. Even in 1910 and 1912 when we again discussed this sub-

of the majority occasional voices were raised. Colombo of Cremona in 1559 declared that monstrosities were not due to the devil or to sodomy but were the result of faulty development. A cogent argument against maternal impressions according to Blondel in 1727 was the fact that illegitimate mothers could not destroy their offspring by their most intense wishing.

Belief in the mysterious influence of mind over matter has come down to the present generation, and we find one of our founders, the first president of this society, Fordyce Barker, a convinced advocate of the doctrine of maternal impressions. At the meeting of the American Gynecological Society in 1886 he reported several instances of deformities produced in this way. In the discussion that followed Bussey narrated 41 additional cases. Only one man raised his voice in opposition, John S. Billings, who said that such effects ran counter to all our knowledge of the physiology of pregnancy and hence we must simply say: "we do not know." A resolution was passed to have the question investigated by a special committee of three but our transactions do not record the report of that committee. Hirst's *Obstetrics* in 1888 stated that maternal impressions were a proved fact and even as late as 1902 Dickinson-Norris' textbook conceded them as a probability. The studies on pathologic embryology by Mall and Streeter have now shown the fallacy of these theories and point the way to methods of prevention.

The most important chapter in this story of prenatal care deals with the prevention of eclampsia and its associated toxemia. Previous to the middle of the nineteenth century the diagnosis and prevention of impending eclampsia was based wholly on clinical observations. Textbooks are full of accurate descriptions, vividly portrayed, of the premonitory symptoms. Dewees relates of a rapidly fatal case in which the patient suddenly cried out: "My head! My head!" and fell into convulsions. Epigastric pain, tingling of the ears, blind spots, and edema of the face and hands were evidence of plethora, and bleeding would alone prevent the eclamptic outburst.

It was in 1843 that J. C. Lever in England first noted the constant presence of albumin in the urine of patients with eclampsia or pre-eclamptic symptoms. At about the same time in France, Rayer, followed by Blot, Labat and Mayer Cahen noted the constancy of these findings. It was not long until the urine of every patient with edema or headache was examined and the appropriate treatment instituted where albumin was found. James Simpson of Edinburgh confirmed the uniform presence of albuminuria in eclamptic patients and in 1859 concluded that "albuminuria, dropsy, and convulsions are successive effects of one common central cause—viz, a pathologic state of the blood, to the occurrence of which pregnancy in some way peculiarly predisposes."

In the fully organized obstetrical services of the Scandinavian countries and Holland the establishment of proper prenatal care through midwives and physicians was relatively simple. In Holland according to Dr. DeSnoo the work has been done individually with each patient through the person in attendance, rather than through a general prenatal clinic as elsewhere. Soviet Russia has devoted special consideration to the care of the expectant mother. On a nationwide scale it has established centers for maternal welfare where patients are instructed and examined. This is one of the big accomplishments of the present government.

In France Pinard led the movement for prenatal care. The interruptions of the Great War were partly compensated by the splendid cooperation of American physicians at the time of its conclusion in 1918. Dr. Fred Adair was in charge of a portion of this prenatal work during these years and the experiences gained there stood him in good stead when he took over the chairmanship of the Committee on Maternal Welfare in this country. This committee's activities were the indirect outgrowth of the Conference on the Prevention of Infant Mortality held at New Haven in 1909. The work progressed rapidly and by 1915 Whitridge Williams prepared a model prenatal record sheet. "The best results in prenatal care are obtained," he says, "when work is begun in the obstetric dispensary of a well-regulated hospital, continued in the lying-in wards and completed by the children's hospital with its milk fund and baby saving devices."

In 1920 a committee of three was appointed by the American Gynecological Society to confer with similar committees appointed by the American Pediatric Society and the American Child Health Association to plan for the development of a maternal and child welfare program in the United States. The splendid work of this committee and its successors is too recent to need amplification here. Its influence was made nationwide by the publicity and the illuminating studies that grew out of the White House Conference of 1931, studies in which the Fellows of our Society took a distinguished part.

At the present time I think it is not an idle boast that in spite of the handicaps arising from our vast territory, the admixture of various races, especially negroes, and the heterodox requirements for medical practice, we have succeeded in this country in developing one of the best organized systems for prenatal care in the world. It is a chapter in our obstetric development of which we have reason to be proud.

Such in brief is the history of prenatal care. In conclusion may I recall to your mind one episode from this record that should have a special significance for us at the present time. I refer to the discovery of blood pressure elevation as an index of threatened convulsions. In 1905 the Fellows of our Society gathered for a symposium on eclampsia.

ject, only Hirst and Polak stressed the usefulness of blood pressure readings. In Europe, in spite of additional work by Vaquez, Wiener and others, the compendious *Handbuch* of von Winekel in 1907 fails to recognize the value of blood pressure measurements in eclampsia. It was not in fact until twenty years after Vinay's first work that the true significance of these findings was generally appreciated.

The establishment of special clinics for prenatal care on a nationwide scale under university, hospital, or municipal administration dates back to the beginning of this century. Previous to 1900 we had only one such clinic, that already mentioned at the Dublin Maternity established in 1858. The man who first visualized the possibilities of prenatal care thus organized under hospital supervision was James Ballantyne of Edinburgh. Influenced by many years of study in antenatal pathology, he urged the establishment of a prematernity ward for the care and study of pregnancy complications. By dint of persistence the one bed provided at the Royal Maternity Hospital in 1901 for these investigations grew to a 23-bed ward two decades later. Ballantyne in addition to being a great scientist and clinician had in him the strain of a visionary. The dawn of the twentieth century found his spirits rising with the hope of an age when all expectant mothers would be properly cared for. In fantastic mood he pictures the perfect prematernity institution of the future. It is situated in the town of Weissnichtstadt, somewhere on neutral ground between France and Germany, built by the munificence of an American millionaire, and officered by an international staff. Over the doorway runs the legend: "Teach us what we shall do unto the child that shall be born." In one ward abortions and premature labors are being prevented. In another, the so-called "hall of the innocents," syphilis in the pregnant mother is being eradicated. The room whose doorway is labeled "Heredity" contains a hemophiliac who is being cured by some new method. In the Roentgen room the art of prenatal diagnosis is being perfected. Many of these dreams of Ballantyne have indeed come to pass. Only the concluding remarks of the physician-in-charge sound strangely incongruous at the present time. Ballantyne puts these words into his mouth: "In this twentieth century we prevent everything—war, disease, hurricanes—everything except the doing of good to others." We are thankful that Ballantyne did not live to see how far this Utopian vision is from being fulfilled.

In England the movement for prenatal care was greatly aided by the National Health Insurance acts of 1911 and 1913, providing for maternity benefits. In 1914 the local Government Board issued a circular offering a grant to local authorities for antenatal care. This included: (1) local supervision of midwives, (2) antenatal clinics, (3) home visiting of expectant mothers, (4) provision in hospitals for treatment of the complications of pregnancy. By 1927 there were already in existence 600 prenatal clinics in England alone.

SARCOMA OF THE UTERUS*

CLINICAL AND PATHOLOGIC STUDY OF FIFTY-NINE CASES

EMIL NOVAK, M.D., BALTIMORE, MD., AND DAVID FYFE ANDERSON, M.D.,
GLASGOW, SCOTLAND

(From the Department of Gynecology, Johns Hopkins Medical School)

SARCOMA of the uterus is so much less common than carcinoma of the same organ that it is not surprising that it has received far less attention in the literature. Most of the publications on the subject have dealt with reports of single cases or small groups of cases, as might perhaps be expected from the paucity of material in any but the larger clinics and laboratories. Our knowledge of many of the features of uterine sarcoma is still very incomplete, though it has been recognized as a clinical and pathologic entity since 1860, when the first case was reported to the Berlin Obstetrical Society by C. Meyer. No less a personage than Rudolf Virchow made the pathologic report on this case, and an accurate description of uterine sarcoma of the endometrial type was incorporated in his *Krankhafte Geschwülste*, published in 1865. In the seventy-seven years since Meyer's report only a relatively small group of contributions may be said to have represented serious efforts to add to our knowledge of this subject.

It has therefore seemed worthwhile to study the comparatively large material which has passed through our laboratory, the present report covering a period of twenty-five years (1911-1935 inclusive). During this time, in a total of 26,973 case specimens, 59 cases of uterine sarcoma have been encountered. These have been studied from both a clinical and a pathologic standpoint, for only by such a correlation can one expect to extract the fullest information as to the characteristics of this disease. We have been fortunate in having follow-up information on 50 of our 59 cases, in spite of the fact that 18 specimens or sections came to our laboratory from outside clinics, meaning usually considerable difficulty in getting information as to the postoperative careers of the patients.

In an excellent paper before this Society in 1934, Kimbrough presented an analysis of 43 cases of sarcoma of the uterus, more especially from the standpoint of the factors which influence the end-results. The reader may be referred to this paper for a résumé of the literature on this and other clinical aspects of the problem. While in our present paper we have likewise included an analysis of the clinical characteris-

*Read at the Sixty-Second Annual Meeting of the American Gynecological Society, held in Swampscott, Mass., May 31 to June 2, 1927.

Dr. Anderson's Participation in this study was made possible through the tenure of a Rockefeller Fellowship.

French and German medical journals had for ten years previously contained important contributions on the subject of hypertension in eclampsia. In our own country Cook and Briggs had made careful observations on high blood pressure associated with eclampsia as early as 1903. Yet by no word or suggestion was this fundamental advance recognized in our discussion of the subject. I bring this up not in a spirit of criticism but to ask you here today to consider whether we may not in similar manner be overlooking discoveries, already made, but whose value we have not fully recognized. As Fellows of this Society, is it not our responsibility, not merely to add to the sum-total of scientific knowledge by our own investigations, but also to develop our critical faculties, so that we may become discerners of the truth, able to pick the grain from the chaff, and ever alert to recognize great discoveries promptly when they are made? By so doing, we shall materially hasten the progress of medicine.

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of corporeal as compared with cervical myomas will no doubt explain in part at least the predilection of sarcoma for the corpus uteri.

The symptomatology is not distinctive, so that in most cases the diagnosis is not made until operation; or even more frequently, not until the pathologic examination. Abnormal bleeding may be entirely absent, especially when the endometrium is not involved. On the other hand it may be of great significance, especially when it occurs after the menopause, and particularly when in these postmenopausal cases the uterus is the seat of myomatous growths. In younger women there may be either menstrual excess or intermenstrual bleeding, or both. Needless to say the hemorrhage is in any event only suggestive of possible malignancy, and carcinoma will more frequently be found to be its cause than sarcoma.

Abnormal discharge may likewise be a symptom, as in carcinoma. In earlier stages it is likely to be thin and watery, but sooner or later serosanguinolent. Still later it may, as a result of necrosis and ulceration, become quite foul, and may even contain sloughing particles or shreds of tissue. Rapid increase in the size of myomatous tumors, especially when this is associated with bleeding, should likewise suggest the possibility of sarcoma. Pain may be a symptom, though often not until the later infiltrative stages of the disease, when it may be intense and continuous. In these late stages, profound anemia, cachexia and weakness may be noted, making these patients very unfavorable risks for operation. Indeed, one must be struck with the number of patients, in both our own series and that of Kimbrough, in which death occurred within the first few days after operation, throwing into doubt the advisability of operation in such advanced cases.

Still other symptoms, none of them distinctive, may be noted, as will appear from Table III. In some cases diagnostic curettage will establish the diagnosis, as where the disease is polypoid or where the endometrial surface is involved, but when the disease is beneath the surface, microscopic examination of curettings will not be helpful.

TABLE III. SYMPTOMS

SYMPTOMS	NUMBER OF PATIENTS IN 57 CASES
Irregular bleeding	37
Pain, abdominal and pelvic	27
Tumor, abdominal and vaginal	24
Loss of weight	7
Foul, nonhemorrhagic discharge	4
Frequency of micturition	4
Painful defecation	2
General weakness	2
Dysmenorrhea	1

Extension of the disease is by direct continuity, by the blood stream, or by the lymphatics. The hematogenous route is most important in

tics and end-results in our series of cases, we have been perhaps even more interested in the pathologic study of the rather large material at our disposal.

Table I will give some idea of the incidence of sarcoma of the uterus as compared with the other more common uterine lesions encountered in the twenty-five year period under study.

TABLE I. RELATIVE INCIDENCE OF UTERINE SARCOMA AS COMPARED WITH MORE COMMON UTERINE LESIONS OBSERVED IN 26,973 CASE SPECIMENS

DIAGNOSIS	NUMBER OF PATIENTS	INCIDENCE PER CENT
Myoma uteri	6,981	25.9
Adenocarcinoma of fundus	241	0.89
Adenocarcinoma of cervix	88	0.33
Epidermoid carcinoma of cervix	934	3.5
Sarcoma of uterus	59	0.22

Sarcomas, therefore, constituted 4.5 per cent of uterine malignancies (exclusive of chorionepithelioma) encountered during this quarter of a century. If the 18 patients treated in other hospitals be excluded, the incidence of sarcoma of the uterus was 0.15 per cent, and this tumor accounted for 3.1 per cent of uterine malignancies (exclusive of chorionepithelioma). In Kimbrough's investigation, sarcoma constituted 3.2 per cent of uterine malignancies, while Haase found the proportion to be 3.3 per cent, a rather remarkable uniformity in these three large groups of cases.

Clinical Characteristics.—The disease most frequently affects women during the middle period of life, our own series showing the highest incidence during the fifth decade. On the other hand, the rare grape-like sarcoma of the cervix occurs often in infancy.

TABLE II. AGE INCIDENCE

AGE	NUMBER OF PATIENTS	INCIDENCE PER CENT
7 months	1	1.8
2 years	1	1.8
14 years	1	1.8
20-25 years	2	3.5
26-30 years	4	7.0
31-35 years	6	10.5
36-40 years	6	10.5
41-45 years	10	17.5
46-50 years	10	17.5
51-55 years	4	7.0
56-60 years	8	14.0
61-65 years	3	5.2
66-70 years	1	1.8

Any portion of the uterus may be the seat of the tumor, though the body is far more frequently involved than is the cervix. Piquand, for example, found in a collective study of 393 cases that the body of the uterus was involved in 325 and the cervix in 68. The greater frequency

one and a half years after hysterectomy for a myoma in which there was a "suspicion of sarcoma." The histologic examination of the recurrent tumor, however, failed to show any evidence of malignancy, though blocks were made in from 20 to 25 different areas. A third operation was done ten months later for a second recurrence and again the tumor proved to be a myoma with no suspicion of malignant change. Six months later a retroperitoneal recurrence appeared and the examination of this showed areas of polymorphic sarcoma in addition to myomatous elements. The patient died two years later. Neugebauer has also reported a case in which, six years after supravaginal hysterectomy for benign myoma, there were found 3 pelvic tumors entirely separated from the amputation area and all showing the histologic structures of simple benign myoma.

Pathology and Classification.—Much of the older discussion concerning the pathology of sarcoma of the uterus has revolved about the problem of its histogenesis, and more particularly about the question as to whether the sarcoma may arise directly from muscle cells or whether it has its source always in connective tissue elements. Without going into the history of this controversy, suffice it to say that the former of these viewpoints is now the accepted one. As far back as 1894, Williams demonstrated what he considered a direct transition of muscle cells into sarcoma cells, and Kelly and Cullen, as well as other authors, made similar observations. In more recent years there has been much discussion as to whether sarcoma can arise from the mature muscle cells of the uterine wall or of a myoma, or whether it must spring from rests of undifferentiated cells which persist in the uterine wall. Merely to summarize the existing evidence, the majority of leading pathologists agree with Meyer that an origin from fully differentiated muscle cells is unproved and unlikely. This, after all, is the same problem which exists as regards sarcoma and other malignant growths in other parts of the body, with the same preponderance of opinion as to the improbability of the fully differentiated cell being the source of the malignant cell elements.

To hark back for a moment to the question of whether muscle or connective tissue cells are primarily concerned in the histogenesis of sarcoma, it must be remembered that all the constituent elements of the uterus—muscle, connective tissue, epithelium, blood vessels—are of common embryonic ancestry, and all are of mesodermal origin. It would, therefore, be surprising if a malignant connective tissue tumor-like sarcoma could not arise from any one of these elements, or, for that matter, if at times a mixed tumor could not likewise develop, as is actually the case. This, as a matter of fact, represents the preponderant view of leading authorities as to the histogenesis of uterine sarcoma. It may arise from the muscle cells of the uterine wall or of uterine

metastasis, which therefore is more characteristically systemic rather than regional. Among the organs, most frequently the seat of these metastases, are the lungs and liver. In 33 autopsy cases Gessner found metastases in 24, including 15 in the lung, 10 in the liver, 8 in the intestine, 5 in the omentum, 5 in the kidney, 5 in the pleura, with smaller numbers in other organs, such as the brain, ovaries, heart, etc.

Other clinical data from our own cases are briefly summarized, without further comment, under the following heads: Race, age of puberty, familial incidence of malignant disease, and social status.

RACE

The race of the patient was known in 56 instances. Of these cases of sarcoma of the uterus, 53.6 per cent occurred among white patients and 46.4 per cent among colored women.

Age of Puberty.—Information regarding the menarche could be obtained in only 48 cases, and even at the best this is likely to be lacking in accuracy. In 60.5 per cent of these cases the age of puberty was between twelve and fourteen years.

TABLE IV

AGE	NUMBER OF PATIENTS	INCIDENCE PER CENT
9 years	1	2.1
11 years	4	8.3
12 years	13	27.1
13 years	8	16.7
14 years	8	16.7
15 years	7	14.6
16 years	5	10.4
17 years	1	2.1
18 years	1	2.1

Familial Incidence of Malignant Disease.—Investigation of the family history in 56 cases of sarcoma of the uterus showed that there was no incidence of malignant disease in 53 or 94.6 per cent, while positive evidence was noted in 3 or 5.4 per cent.

TABLE V. SOCIAL STATUS

STATUS	NUMBER OF PATIENTS	PER CENT
Unmarried	5	9.1
Unmarried with pregnancy	1	1.8
Married without pregnancy	6	10.9
Married with pregnancy	43	78.2

“Recurrent Fibroids.”—In the older literature one finds frequent reference to “recurrent fibroids” and to malignant myomas with the capacity to recur and to metastasize. There can be little doubt that these growths were really types of sarcoma, and yet in a number of reported cases, vagaries of behavior have been described which are difficult of explanation on general pathologic grounds. In a case reported from Halban’s clinic by Christophorakos, recurrence occurred

tion, with the use of terms which aim at greater descriptive precision as to the constituent cells and their probable histogenesis, have been suggested, but they are of more value in the hands of experts than in those of the average pathologist. For example, such terms as sarcoma myoglobiellulare, sarcoma myofusciellulare, and sarcoma myocellulare are employed by Meyer in the grouping of myogenic sarcoma on the basis of histogenesis and degree of cell maturity.

All such classifications, however, have the weakness that in an evitable and not small proportion of cases the pathologist cannot be sure of the exact histogenesis. Moreover, in this method of classification, as well as in the simpler one more generally employed, viz., into round, spindle or mixed cell types, one cannot eliminate the individual factor in inter-

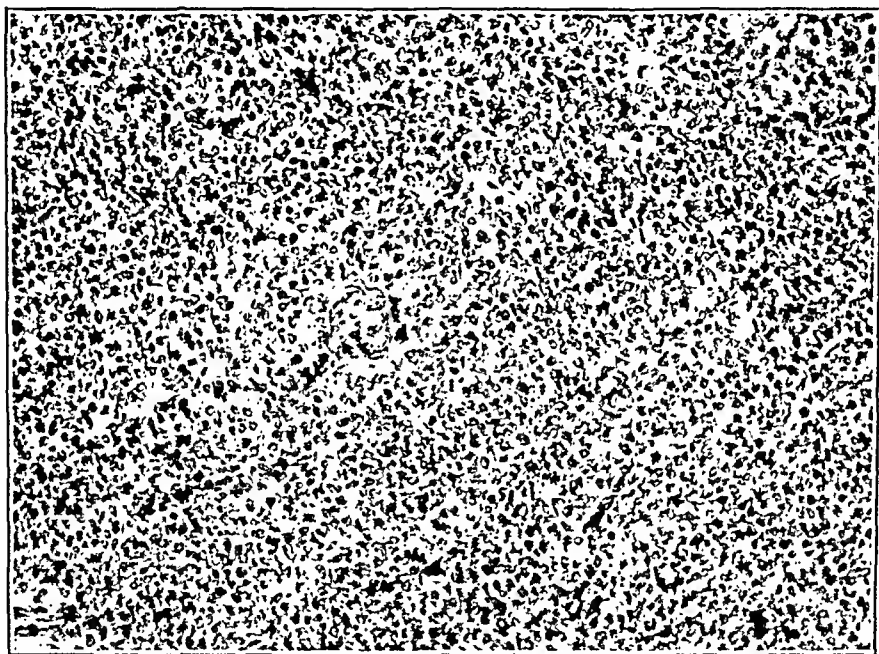


Fig. 2.—Round cell sarcoma in patient of forty-nine years, well eighteen years after operation, followed by radiation.

pretation. For example, in the spindle cell variety many of the cell bundles are cut transversely, producing a round cell picture in such areas, and leading often to the diagnosis of mixed cell sarcoma. To obviate this, Meyer makes the useful suggestion that the course of the blood vessels may serve as a valuable guide. If for instance, in an area in which blood vessels are observed in longitudinal section, the cell type is round, the diagnosis of round cell sarcoma would be justified, whereas round cell areas without such histologic control might well be cross-sections of spindle cells. Even with allowance for such factors, however, there is no doubt that the cell type in different tumors and even in different parts of the same tumor may show all grades of differentiation, from a very immature type of round cell to a fusiform

myomas, or from the connective tissue elements in the uterine wall, or in myomas, or in the endometrium, or from the walls of the blood vessels of the uterus.

It is on these grounds that we base the usual classification of sarcomas into (1) those arising in the muscle or connective tissue of the uterine wall, (2) those arising in myomas of either the corpus or cervix, (3) those arising in the mucous membrane of either the corpus or cervix, (4) those arising in the blood vessel apparatus. An origin from any of these sources is possible and in individual cases has been demonstrated; but, unfortunately, in a very large proportion of cases which come to study, it is not possible to do more than conjecture as to the origin, and in many cases even conjectures seem hopeless. No matter

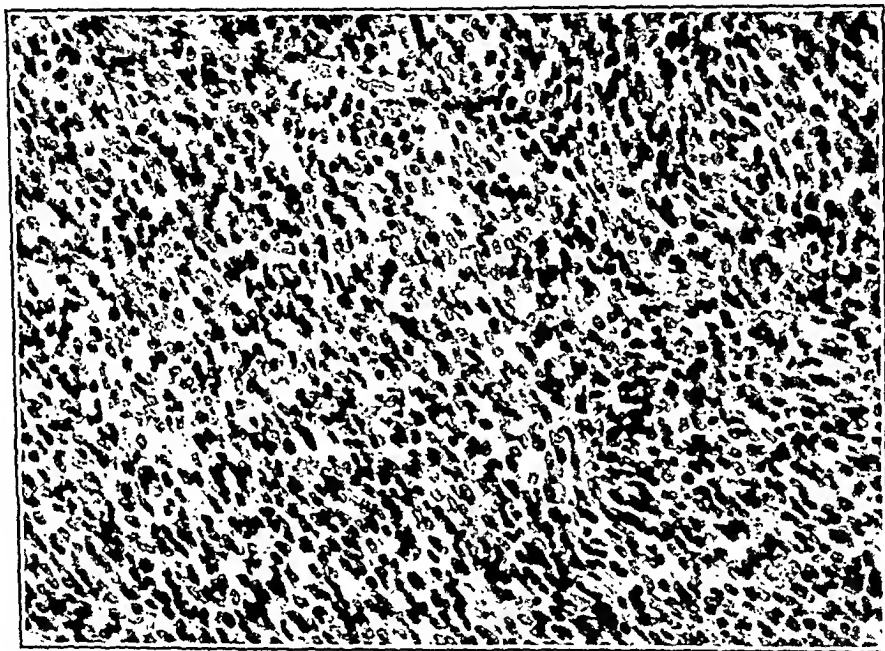


Fig. 1.—Sarcoma of dominantly small spindle cell type in patient of sixty-five years, reported well several years after operation.

what the origin, the invasive tendencies of sarcoma tend soon to blot out the evidence for this, and morphologic differences are all too often insufficient to establish the histogenesis of many advanced cases.

The uncertainties in classifying many cases, together with the rather limited practical value of such classifications, make it seem more important, with some reservations as regards special types, to lay more stress upon classifications dependent on cell type and degree of cell differentiation, because of the conceded importance of such variations as indicators of the relative malignancy of tumors in general.

It seems to us, therefore, that the time-honored division of sarcomas into the spindle cell (Fig. 1), round cell (Fig. 2), and mixed cell groups is as serviceable as any in the classification of uterine sarcoma. To these we might add a giant cell variety. Refinements of this classifica-

gest a special histogenesis, for which opinion there is histologic support. This grapelike sarcoma presents as a grapelike mass of pinkish, edematous polyps involving the cervix and usually also the upper vagina. In advanced cases the entire vaginal canal may be filled, with widespread lateral infiltration of the whole pelvis. The disease is always fatal. Of especial interest, however, is the fact that among the sarcomatous elements one may find also other mesodermal elements, especially embryonic striped muscle, with, less frequently, cartilage.

While mixed tumors of the uterine body also occur, this teratoma-like mixture is much more frequent in the small cervical group of botryoid tumors, lending support to the theory that they are of teratoid nature. Because of the rarity of these tumors, a brief report of the two cases in our present series seems justified.

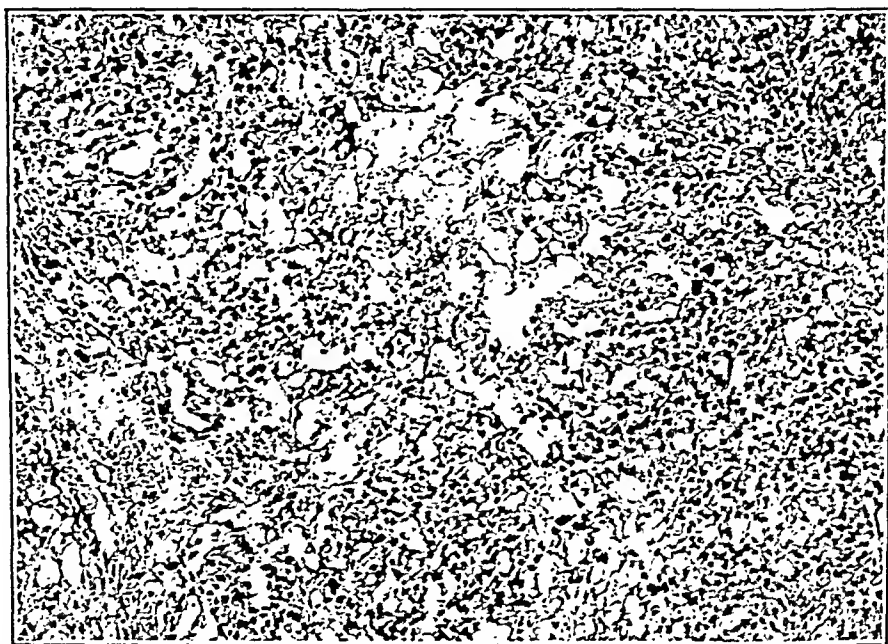


Fig. 3.—Sarcoma botryoides (kindness of Dr. José Medina, Sao Paulo) in infant of seven months.

CASE 1.—This specimen was sent to one of us (Novak) for pathologic examination by Dr. José Medina, of Sao Paulo, Brazil. It was obtained by biopsy from a polypoid tumor which filled the vaginal fornix, presumably arising from the cervix. The patient was an infant of seven months. The tumor was described as friable and very vascular. The child died, but autopsy was not obtainable.

The histologic examination, as will be seen from Fig. 3, shows the tumor to be made up of cells chiefly of spindle type, arranged for the most part around small spaces which are evidently lymph channels. The cells themselves show only a rather low degree of anaplastic change, though many of the nuclei are rather large and heavily stained. There is no evidence of unstriped muscle or of other teratoid elements. The more superficial parts of the tumor show extensive necrosis and inflammatory infiltration.

CASE 2.—The patient was a child of two, who for six months had had vaginal bleeding, with the occasional passage of small polypoid masses from the vagina.

cell scarcely distinguishable from the normal. The round cell variety is relatively rare as compared with the spindle or mixed cell type.

The *gross characteristics* of sarcoma of the uterus show great variation, depending especially upon histogenesis and location. In the most frequent type, that arising in uterine myoma, the sarcomatous change often brings about a sufficiently definite macroscopic alteration to justify a presumptive diagnosis of sarcoma; in others the change is much less marked, so that sarcoma will not be suspected until microscopic examination. The sarcoma areas occur most frequently near the center of myomas, but may at times be noted only in the periphery. Instead of the hard rather glistening cut surface of a typical myoma, with its characteristic whorl-like appearance, the sarcoma areas present either the "raw-pork" appearance described by Cullen, or, when necrotic changes are more marked, they present as brain-like pulsatous, broken-down areas, with often a ragged cavity formation and perhaps hemorrhage. The common hyaline degeneration of benign myomas may at times lead to confusion, as it may bring about rather large areas of amorphous appearance, in which the characteristic architecture of myoma is likewise lost. However, the consistency is likely to be firmer than that of sarcoma unless there is also present the easily recognizable cystic degeneration.

Mural sarcomas may at times also arise as nodular and fairly circumscribed tumors, so that it may be difficult to be sure whether or not the tumor was preceded by a benign myoma. More often, however, they are much more diffuse in their growth, so much so that they may produce a fairly uniform enlargement of the uterus, which may even resemble an early pregnancy. The same thing is true of the diffuse varieties arising from the endometrial stroma.

The endometrial sarcoma not infrequently assumes a polypoid architecture, and this is likewise true of growths originating from the mucosa of the cervix. As a matter of fact, the superficial cervical sarcomas may be mistaken for benign polyps, as in one of our own cases, in which sarcoma was not suspected before microscopic examination. As a rule, however, the polyps are bulkier, denser, and more friable than the common benign variety. In other cervical sarcomas, there may be widespread ulceration and infiltration, producing a picture not distinguishable from the far more common carcinoma in its advanced stages.

Finally, a word as to the rare grapelike sarcoma of the cervix (sarcoma botryoides), particularly as our series includes two specimens of this lesion. This grapelike tumor (traubiges Sarcom) was described by Spiegelberg as far back as 1897, under the designation "sarcoma colli uteri hydropicum papillare," and various other names have been applied to it by other authors. From a clinical viewpoint, the most interesting feature of this disease is that while it may occur in adults it has often been noted in infants, and this age predilection would sug-

Microscopic Characteristics.—With reference to the microscopic appearance of uterine sarcoma, it is scarcely necessary to go into detail, inasmuch as the same wide variation in cell morphology occurs which characterizes sarcoma in general, and, as we have already mentioned, there may be much variation in different parts of the same tumor with regard to the degree of de-differentiation of the constituent cells. The pattern and architecture likewise present much individual variation, some growths being very cellular and diffuse, others having an alveolar or plexiform pattern (Fig. 6), while in rare cases the relation to the blood vessels justifies the designation of angiosarcoma (Fig. 7). The alveolar pattern seems in most cases to be imparted by the presence of subdividing masses of connective tissue usually showing extensive hyaline degeneration.

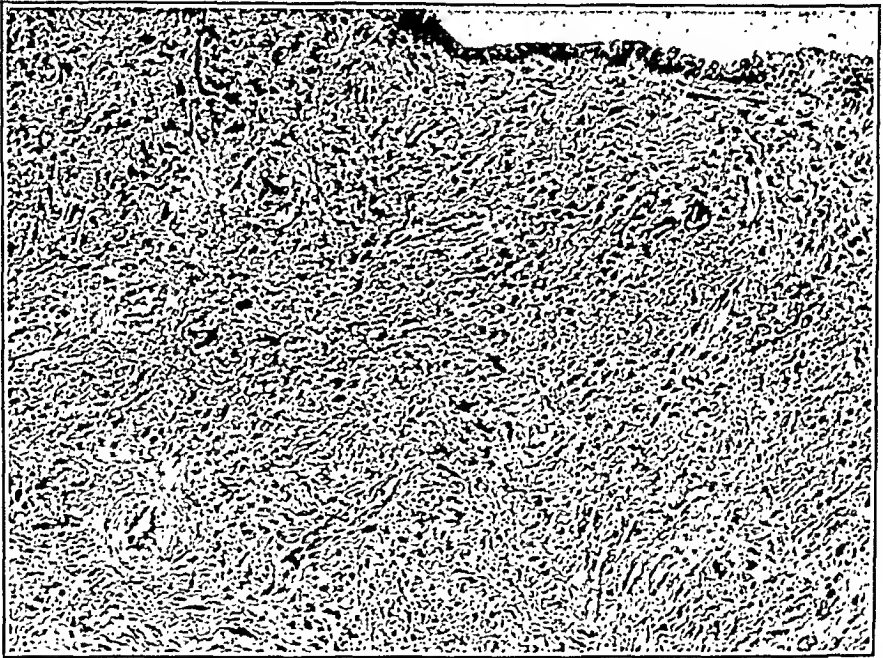


Fig. 5.—Polypoid cervical sarcoma in patient of thirty-eight years. (Kindness of Dr. Karl M. Wilson, Rochester, N. Y.)

In many myogenic tumors there appears to be an insensible transition from normal muscle cells to the malignant cells, and in some tumors the constituent cells show only mild degrees of departure from the mature muscle cells. In others, though the cells may still be definitely spindle-shaped, there is a marked degree of anaplasia, with much hyperchromatism, frequent mitoses, and often giant cells.

The term giant cell sarcoma is often employed, but the significance of such elements is not always the same. In perhaps the majority of cases giant cells are found in tumor areas which are obviously degenerating, and it seems clear, from the study of transition stages, that the large giant cells, often polynuclear, are formed from the cytoplasmic confluence of degenerating sarcoma cells (Figs. 8 and 9). One usually

The cervix is said to have been amputated at another hospital some time previously, and she had had two radium treatments (dosage not known). She had, however, become progressively worse, with the development of cachexia, together with a severe pyelitis. The tissue which came to our laboratory, through the kindness of Dr. Margaret Handy, of Wilmington, Delaware, consisted of two small polypoid masses expelled from the patient's vagina and showing typical sarcoma (Fig. 4). The case terminated fatally a short time later.

A third case, representing a cervical polypoid sarcoma in an adult, was not of the typical botryoid variety, but it is of sufficient interest to justify brief mention.

CASE 3.—This case we are permitted to include in our series through the kindness of Dr. Karl M. Wilson, Professor of Obstetrics and Gynecology at the University of Rochester School of Medicine and Dentistry, who was good enough to send us slides for examination. This patient was thirty-eight years old. Seven years previously she had been given x-ray treatments because of uterine bleeding, and

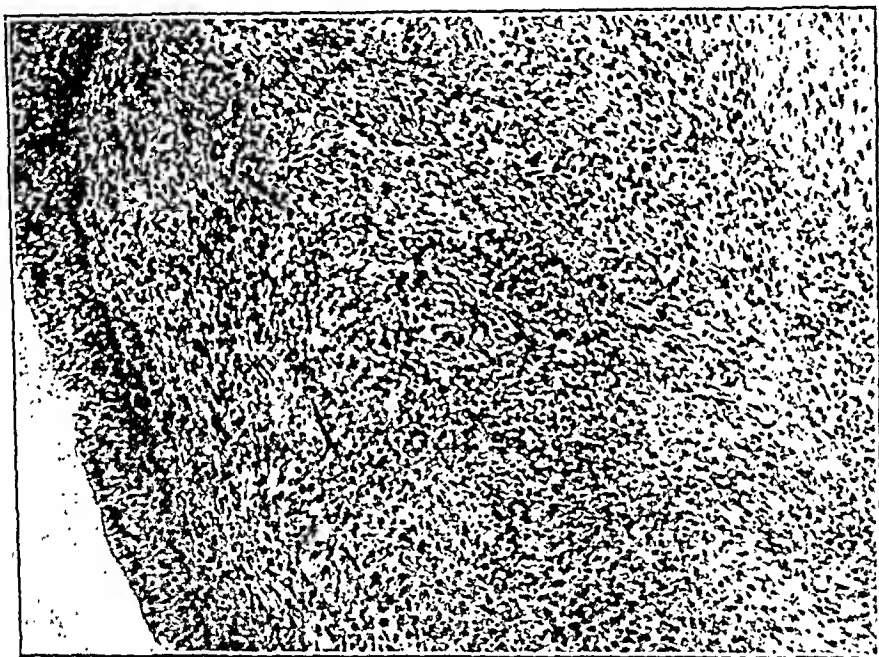


Fig. 4.—Sarcoma botryoides in child of two years. (Case of Dr. Margaret Handy, Wilmington, Del.)

complete amenorrhea had ensued. For two months before being seen, however, she had bled almost constantly. On examination a polypoid growth was found in the cervix. According to Dr. Wilson's note, "the growth bled on touch, presented a rather offensive odor, and suggested a necrosing polyp or a small submucous myoma." This was removed by the vaginal route.

The histologic examination shows a finely lobulated polypoid tumor which apparently arose from the cervix, as stratified squamous tissue covers the sarcoma in some places, while in others the small polyps are covered with cervical and even with endometrial epithelium. In the latter areas, the subepithelial cells resemble a highly active endometrial stroma, with numerous mitotic figures, often as many as six or eight in a high power field. In the lower portion of the growth (Fig. 5), where the covering epithelium is of the stratified squamous type, the cells are larger, spindle-shaped, with many giant nuclei, few mitoses, and extensive degeneration. The growth is evidently a polypoid cervical sarcoma of mucous membrane origin.

which must be looked upon as an indication of abnormal cell activity (Fig. 10). Frequently, though not by any means always, such tumors also exhibit numerous mitoses.

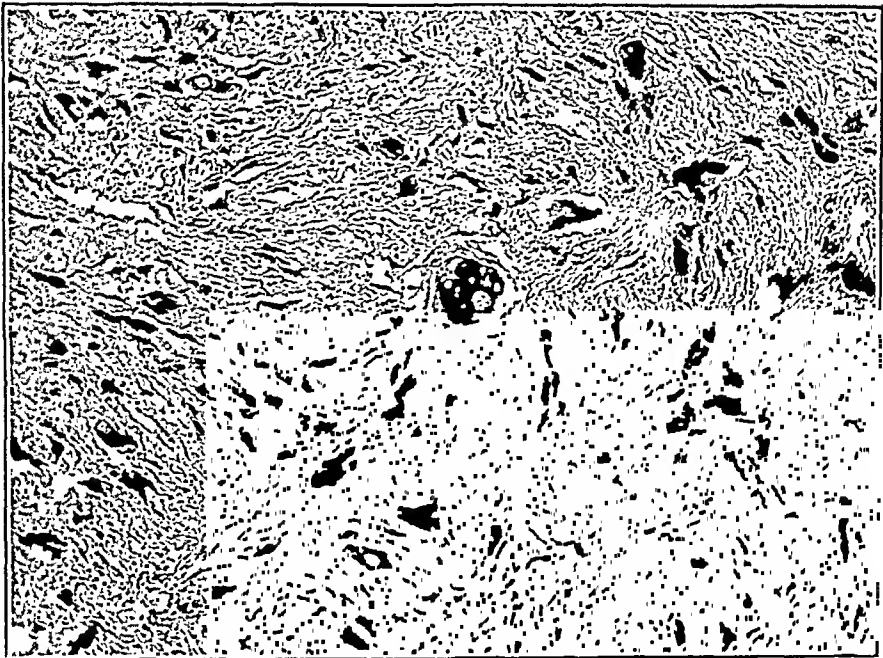


Fig. 8.—Giant cells of symplasmic type, due to degeneration process.

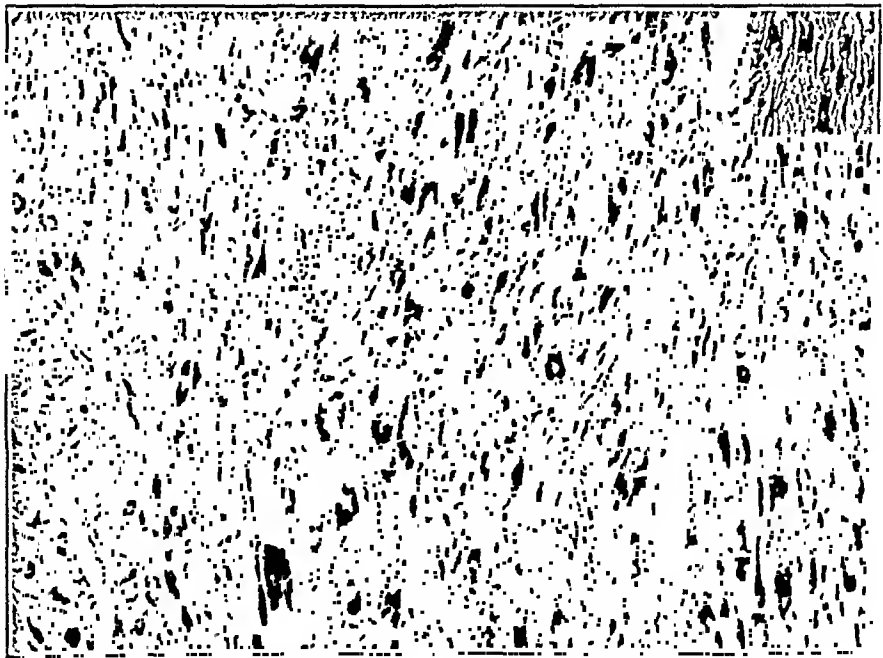


Fig. 9.—Degenerative type of giant cell formation.

As an important index of the degree of malignancy of uterine sarcomas, much stress has in recent years been put upon the nuclear behavior, and especially upon the relative number of mitoses which may be

finds little evidence of nuclear activity in such areas, while in other parts of the same tumor the picture may be quite different, with marked anaplastic cell changes, many mitoses, and often no giant cells.

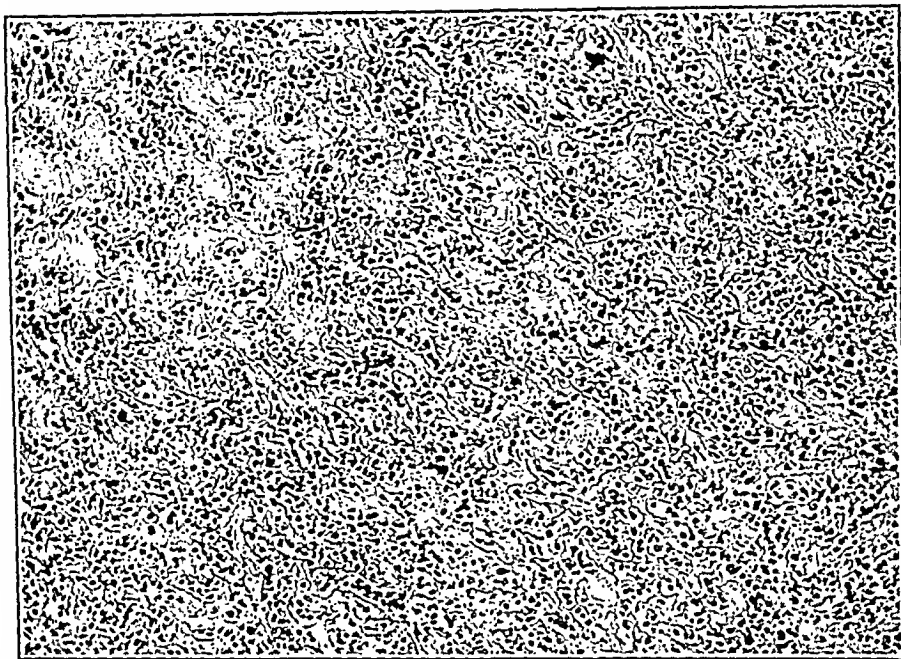


Fig. 6.—Sarcoma of alveolar pattern, with septa of hyalinized fibrous tissue dividing the tumor cells. Patient, aged forty-six years, living and well several years after operation.

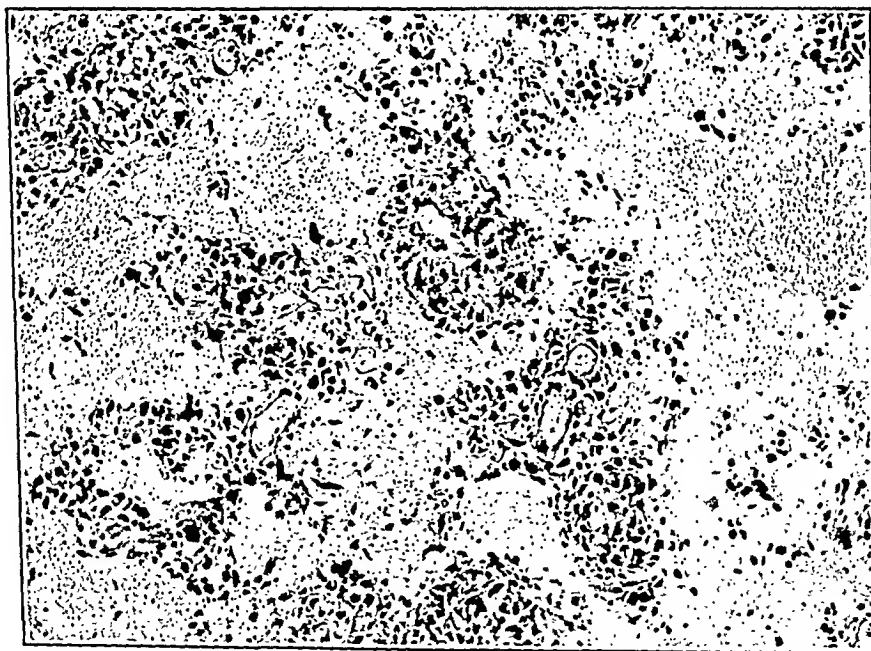


Fig. 7.—Angiosarcoma in patient of forty-two years. Growth far advanced, with loss of 110 pounds in weight, and death soon after operation.

There are, however, other cases in which the designation of giant cell tumors would seem more justifiable, because in these the large giant nuclei are sharply and intensely stained, evidencing a hyperchromatosis

we have adopted in our own study, 20 separate high power fields being counted for mitotic figures. We are inclined to believe that the results of this are not widely different from those which would be obtained had we employed the more intricate technique of counting suggested by Evans.

Mitosis counts were made in all our cases except those in which only one section was available, with too small an area of sarcoma to permit of the study of 20 suitable high power fields, and those where extensive degenerative changes would make mitosis studies valueless. In all, 41 of our cases lent themselves for study along these lines, yielding mitosis counts varying from 0 to 88 in 20 high power fields. As might be expected, and as both Evans and Kimbrough found, the degree of nuclear activity as indicated by the mitosis counts parallels in a general way the degree of clinical malignancy manifested by the tumor. Indeed, the parallelism is quite remarkable.

Of 20 cases in which from 0 to 5 mitoses (inclusive) were found in 20 fields, 15 were living more than three years after operation, 1 died of recurrence ten years after operation, 1 received only palliative treatment and presumably died, and 3 were not traceable. Of 4 patients with between 6 and 10 mitoses (inclusive), 2 were well and 2 died (seven months and five years after operation). Of 4 with between 11 and 20 mitoses, 1 died after ten years of an intercurrent disease, and the 3 remaining were dead, three weeks (sepsis), five weeks (sepsis), and seven months after operation. Of 6 patients with from 21 to 30 mitoses (inclusive), 1 was reported well six months after operation but has not been traceable since, 3 were dead (seventy-two hours, seven months, and seven years after operation), and 2 could not be traced. Finally, of 7 patients with mitosis counts above 30 (up to 88), 4 are known to have died (one day, seven months, 2 at nine months), and the remaining 3 presumably died soon after discharge from the hospital, for all 3 were far advanced, receiving only palliative treatment.

A fact which has interested us is that, with one or two exceptions, the patients with very low mitosis counts, in which recovery was the rule, were those in which the tumor developed in myomas, and in which it was of the spindle cell or mixed cell type, with few or no mitoses. This, fortunately, is the most common variety of sarcoma developing in myoma, and explains why so many cures have followed simple supravaginal hysterectomy, and why sarcoma recurrence is so rare after radiation treatment of myomas. In a minority of cases, however, myomas may be the origin of the more malignant types, though the latter are much more commonly seen when the tumor arises in the musculature or the mucous membrane of the uterus. To put it another way, sarcoma of the uterus may be either of a relatively low grade of malignancy or it may be of a very malignant type, and the proportion of the former is much greater among growths developing in myomas than in those developing in the uterine mucosa or musculature.

present. It would seem quite certain, on general pathologic grounds, that this criterion is of importance.

In a paper published in 1919, Proper and Simpson suggested a classification into 3 types (I, II, III) according to the degree of maturity of the constituent cells. In their own cases the clinical malignancy seemed to parallel the degree of cell immaturity. For example, of their 11 cases of Type III, only 1 was well (though only six months had elapsed since the operation), 1 had a recurrence, 2 died soon after operation, and 7 died of recurrences in from six to eleven months after operation.

Renewed interest in the question of mitotic activity was awakened by the paper of Evans in 1920. In a study of "malignant myomas" he concluded that the degree of mitotic activity parallels the clinical

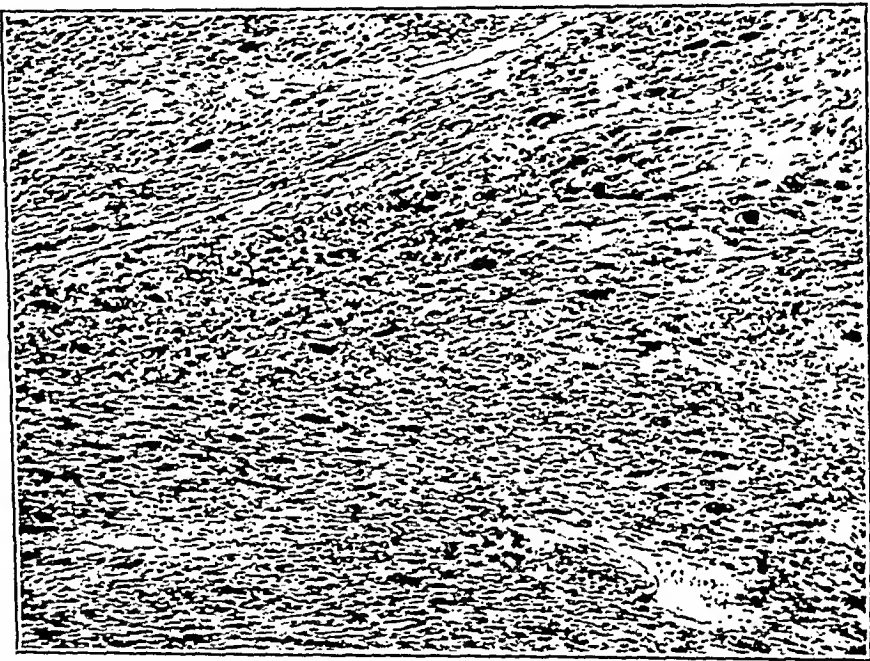


Fig. 10.—Giant cells in actively growing tumor of spindle cell type. Patient, aged sixty-six years, died on thirteenth postoperative day, of pyelonephritis.

malignancy of these tumors. He based his estimates of nuclear activity upon actual mitosis counts by a technique not unlike that employed in blood counts. It should be remembered, however, that such a method can be of considerable value only when the pathologic technique is a very standardized one. The rapidity of fixation, the thickness of the sections and other such factors are so variable in the average group of cases studied that there could be no mathematical accuracy in mitosis counts of this sort. This would apply to such a series of cases as ours, going back over twenty-five years and including many cases from outside sources. It would seem to be just as serviceable and perhaps approximately as accurate in giving an idea of the degree of nuclear activity to count the mitoses in a considerable number of fields from as many different parts of the tumor as possible. This is the plan which

point. For this reason, we can claim no accuracy in our effort to classify our cases according to their origin; viz., (1) 39 in myomas; (2) 11 in the uterine wall; (3) 5 in the endometrium; and (4) 4 in the cervix.

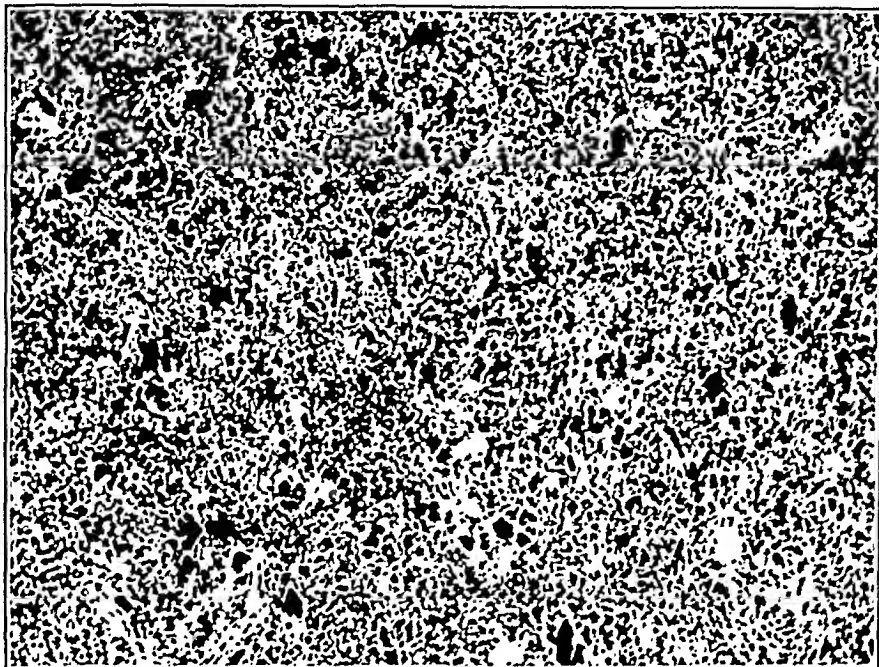


Fig. 12.—Endometrial sarcoma in patient of twenty-eight years of age, with death nine months after radical operation.

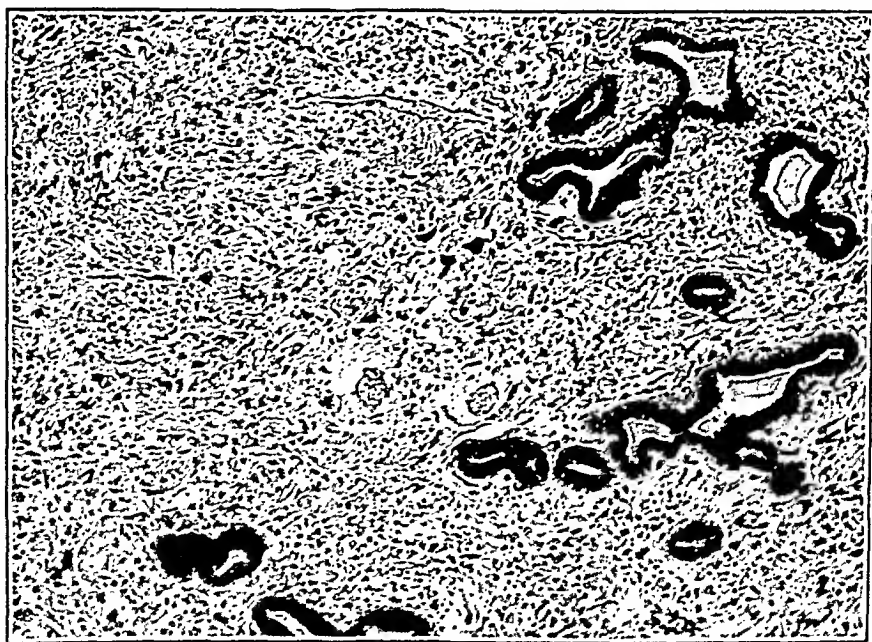


Fig. 13.—Endometrial sarcoma of malignant type, with many hyperchromatic nuclei and numerous mitoses. Patient aged fifty-three years.

In our own series of 59 cases, it was considered that in 39, or 66.1 per cent, the sarcoma was secondary in myomas. This gives an incidence of 0.56 per cent of sarcomatous degeneration in the 6,981 myomas com-

With reference to the much discussed question of the incidence of sarcomatous changes in myomas, the wide discrepancies of figures formerly quoted have given way to a reasonable degree of uniformity in more recent statistics based on a clearer recognition of the histologic criteria of malignancy. The most common mistake of the earlier authors was to mistake very cellular but benign myomas for spindle cell sarcoma, so that in some series an incidence of as much as 10 per cent of malignancy was reported (Werner). It is not always easy to be sure whether or not sarcoma is secondary to benign myoma. The mere presence of myomas does not justify this assumption, and, moreover, it must be remembered that sarcoma may arise as a rather nodular growth which might simulate a sarcomatous myoma. On the other hand, when a sarcoma is found developing in the interior of a myoma in which one

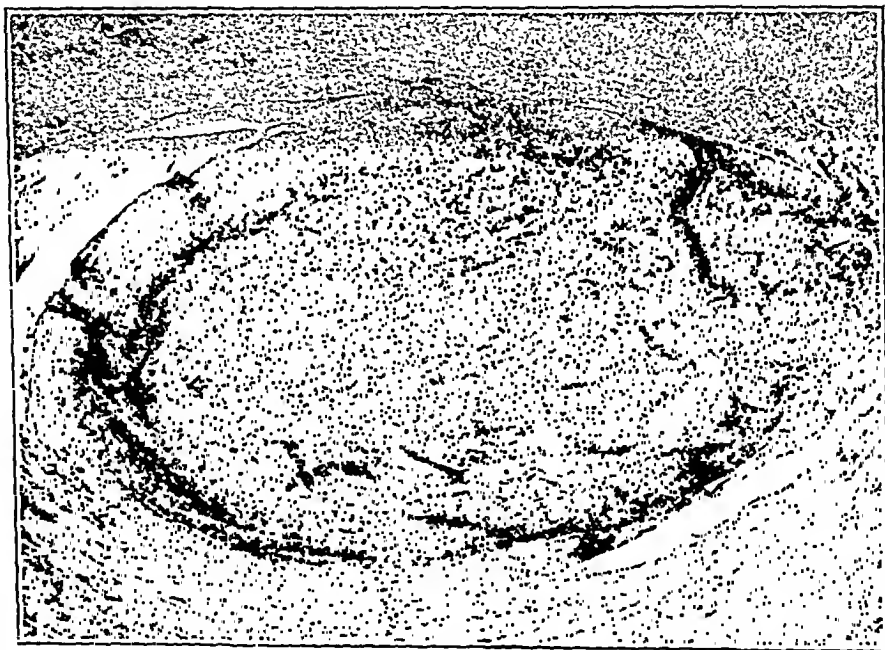


Fig. 11.—Sarcoma nodule developing in myoma. Patient, aged forty-seven years, has remained well after operation.

can still find abundant evidence of the original benign tumor, the origin from such a tumor seems clear (Fig. 11).

The same difficulties arise with reference to sarcoma arising in the mucous membrane. When one finds sarcomatous polyps of the endometrium or endocervix with little or no extension into the musculature, the mucous membrane origin must be accepted. Even in the more invasive types, where the muscularis is invaded, the replacement of the mucous membrane stroma by sarcoma cells, perhaps the presence of sarcomatous polyps, and the direct continuity of the sarcomatous stroma with the sarcomatous invasion of the muscle make the endometrial or endocervical origin reasonably certain (Figs. 12 and 13).

In the late stages of the disease, however, such aids in determining the origin of the tumor are not available, and one can only speculate on this

at least the location of the lesion may make him doubtful as to whether to remove the cervix by a second operation or to depend upon post-operative radiation. With rare exceptions the latter course will probably be the wiser. Indeed, simple supravaginal hysterectomy, without radiation, has cured many cases of undoubted sarcoma. In our own series, many cases have been of this type, the patients' salvation lying in the fact that so many of the sarcomas developing in myomas are in a comparatively early stage and of a relatively low degree of malignancy. The same statement may possibly be made of radiotherapy, though we have no direct evidence on this point. Nothing is more certain than that an inevitable though small proportion of the many fibroids which have been treated by radiotherapy have been complicated by sarcoma, and yet sarcomatous recurrence after such treatment is practically unheard of.

On the other hand, even the most extensive surgery and the most complete radiotherapy will fail to cure the more malignant types of sarcoma when these have reached an advanced stage, as they unfortunately often do, before the patient comes to operation. These advanced cases are poor operative risks as a result of such factors as extreme anemia, cachexia and sepsis. This is indicated by the results shown in Kimbrough's series as well as our own. Palliation is often preferable to operations of the magnitude so often necessary in such advanced cases, assuming that the pathologic diagnosis has been made. In the less advanced and less malignant cases, on the other hand, the preferable plan of treatment is panhysterectomy followed by deep roentgenization.

END-RESULTS

In 50 of our cases it has been possible to secure information as to the postoperative histories. There were 14 patients alive and apparently well for varying periods up to three years following operation. This group, which includes a considerable number of the cases coming from outside sources, was either not traceable beyond three years or, in a few cases, too short a period had elapsed since operation. On the other

TABLE VII. SURVIVAL PERIOD IN FATAL CASES

SURVIVAL PERIOD	NUMBER OF PATIENTS IN 24 CASES
Death following operation:	
Within 14 days	7
5 weeks	1
7 weeks	1
7 months	3
9 months	4
11 months	1
3 years	1
4 years 10 months	1
7 years 2 months	1
10 years	2
Dismissed inoperable, death imminent	2

prised in our material, a figure somewhat lower than the 1.2 per cent of Kelly and Cullen in an earlier study from the same laboratory. It is also somewhat lower than the average reported in the recent literature. Klaften, for example, finds an incidence of 2.8 per cent; Kimbrough, 1.02 per cent; Frankl, 2.02 per cent; Steinhardt, 2.78 per cent; Franz, 0.64 per cent; Brings, 1.94 per cent; and Haase, 4.2 per cent. However, in 72,116 cases of myoma collected from the literature, Vogt found an incidence of only 0.41 per cent of sarcoma.

TREATMENT

Because of the difficulties of diagnosis, the treatment of sarcoma is often a matter of expediency rather than of deliberate planning. Only a few points of special interest need be touched upon here. The methods of treatment used in our own cases are put down simply as a matter of record, with the explanation that some at least were treated before the development of modern radio-therapy, so often a useful present-day adjunct.

TABLE VI

OPERATION	NUMBER OF PATIENTS	DEATHS WITHIN FIVE YEARS	
		NUMBER OF PATIENTS	PER CENT
Subtotal hysterectomy	29	8	36.4
Total hysterectomy	9	5	22.7
Vaginal myomectomy	4	2	9.1
Dilatation and curettage	4	1	4.5
Biopsy (including exploratory laparotomy)	4	3	13.6
Abdominal myomectomy	3	1	4.5
Removal of cervical polypus	2	-	-
Vaginal hysterectomy	1	1	4.5
Excision of cervix	1	1	4.5

X-ray therapy was employed in 12 cases and radium was applied to the uterus in 10 patients in addition to the operative procedure.

Surgery has been, and still is, the backbone of treatment, especially as so large a proportion of sarcomas are not discovered until operation for supposed myoma, or until the laboratory examination of such supposedly benign tumors. The possibility of sarcomatous change in myomas must always be borne in mind by the surgeon, and it is a wise precaution to cut into the tumor masses as soon as the uterus is removed, for a presumptive diagnosis of sarcoma can often be made from the gross appearance of the cut surface. When there is doubt on this point, frozen sections will often enable the decision to be made. If sarcoma is found or suspected, and especially when the lesion encroaches on the cervix, total hysterectomy is far safer than the supravaginal technique.

An experience which every surgeon of large experience must occasionally have is to receive a pathologic report of sarcoma after supravaginal hysterectomy for presumably benign myoma, and in some of these

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DISCUSSION

DR. WILLIAM P. HEALY, NEW YORK, N. Y.—This Society has had two papers presented on this subject in a short space of time, one by Dr. Kimbrough three years ago, and Dr. Novak's today. Thus we have practically 200 cases from two outstanding institutions, and we may assume that the conclusions of these two papers bring the subject up to date for us.

As to the occurrence of this disease, Vogt, in a series of 72,000-odd cases collected from the literature, found that the incidence of sarcoma in association with myoma was about 0.46 per cent. At the Roosevelt Hospital, where I inquired several days ago, there have been within the last seven years four cases in about 1,200 cases of fibromyoma, or less than half of 1 per cent.

Now as to the prognostic importance of the recognized lesion, there are two general types, clinically and histologically, of sarcoma of the uterus: (1) The rather rare form develops from some portion of the uterus itself, and will be found to be extremely malignant, to contain many mitotic figures, and will be pleomorphic. (2) There are the sarcomas that occur in a previously existing myoma, of much less malignant quality, and these are the cases that I believe give the cures.

It is extraordinary that in these two series, aggregating approximately 200 cases, there have been obtained from 30 to 32 per cent of five-year cures. Dr. Kimbrough's series showed about 34 per cent and Dr. Novak's about 30 per cent. We have no such experience at the Memorial Hospital. Our cases are recognized first elsewhere and referred to, either as recurrent or as untreated. We could find only 23 cases in going through all of our material, and we have but 2 patients alive today. Each of these is a recent case, and each has pulmonary metastases. Hence, we feel the prognosis in sarcoma of the uterus is extremely bad.

We have one very interesting case of a patient under treatment. This patient, a woman less than forty-five years old, developed bloody sputum and a cough twelve months ago. By July, 1936, the diagnosis of a pulmonary tumor had been made through the Board of Health, to which she had been sent for diagnosis of tuberculosis. She was transferred to a cancer institution in the city which confirmed the diagnosis of a pulmonary tumor and discharged the patient as incurable. She finally arrived at the Memorial Hospital in October. A complete physical examination did not show any other lesion except a somewhat enlarged uterus. The patient had, however, had menorrhagia for the previous five months, and by January of this

hand, 15 patients were alive and apparently well five years after operation, representing a five-year salvage of 30 per cent. It should be added, however, that 3 additional deaths occurred within ten years, reducing the ten-year cures to 12, or 24 per cent.

In addition to the 2 cases of sarcoma botryoides, which are always fatal, details as to the survival period were available in the 24 known deaths in this series.

SUMMARY

This study is based upon 59 cases of uterine sarcoma observed in our laboratory during a twenty-five year period, in a total material during that time of 26,972 case specimens, an incidence of 0.22 per cent. The highest age incidence was noted in the fifth decade of life. The symptomatology is not distinctive, and the diagnosis often difficult or impossible until operation and laboratory examination.

Sarcoma may arise from any of the constituent elements of the uterine wall or of uterine myoma, but is commonly of myogenic origin. It is probable, however, that it cannot arise, as was formerly believed, from mature muscle fibers, in spite of the apparent histologic transitions often seen. As with sarcoma elsewhere, its origin is almost certainly from unripe or undifferentiated muscle cell elements. The most common seat of origin is in myomas, the incidence of such change in our series being 0.56 per cent, though most authors have found it to be somewhat greater (1 to 1.5 per cent representing a fair estimate). The difficulties of determining the seat of origin (uterine wall, myoma, or mucous membrane) are discussed in the paper, as are the difficulties of classification. The most serviceable grouping is along general pathologic lines, into round, spindle, mixed, and perhaps, giant cell types.

The degree of mitotic activity is a good index of the degree of clinical malignancy of these tumors, as shown in the study of our own cases. The gross characteristics of uterine sarcoma permit of presumptive diagnosis in at least a proportion of cases. The treatment is often a matter of expediency rather than deliberate planning, especially as the disease is so often recognized only at or after operation. Surgery is therefore the backbone of treatment, with radiotherapy as a valuable adjunct.

While uterine sarcoma is a serious disease, the outlook is relatively good in the group arising in myomas. The mural and endometrial varieties are more unfavorable.

In our own series, a follow-up study was possible in 50 cases. Of these only 15 (30 per cent) were known to be living at the end of five years, and only 12 (24 per cent) at the end of ten years.

THE CLINICAL SIGNIFICANCE OF ENDOMETRIAL HYPERPLASIA*

FRANKLIN L. PAYNE, M.D., PHILADELPHIA, PA.

AMONG the many points to be considered in appraising the clinical importance of endometrial hyperplasia are its rôle in benign uterine hemorrhage, whether it be functional or that associated with pelvic lesions, its relation to uterine myomas and endometriosis, its occurrence after the menopause, either with or without demonstrable pelvic pathology, and the part it plays in the development of fundal malignancy. The material for this study consists of 534 specimens of hyperplasia which were collected from 2,070 endometrial sections in the Laboratory of Obstetrics and Gynecology of the Hospital of the University of Pennsylvania. The specimens are divided into two groups, the premenopausal comprising 496 sections and the postmenopausal of 38.

PREMENOPAUSAL HYPERPLASIA

Endometrial hyperplasia may accompany every type of pelvic condition, with the exception of pregnancy and its complications (Table I).

TABLE I. PREMENOPAUSAL HYPERPLASIA, DISTRIBUTION OF 496 SPECIMENS

Functional bleeding	242 (48.8 per cent)
Myoma uteri	146 (29.5 per cent)
Myoma and endometriosis	8 (1.6 per cent)
Myoma and ovarian cyst	10 (2.0 per cent)
Myoma and pelvic inflammatory disease	11 (2.2 per cent)
Endometriosis	6 (1.2 per cent)
Ovarian cyst	13 (2.6 per cent)
Pelvic inflammatory disease	11 (2.2 per cent)
Pelvic floor relaxation	36 (7.3 per cent)
Hyperplasia and fundal carcinoma	8 (1.6 per cent)
Hyperplasia and cervical carcinoma	1 (0.2 per cent)
Functional dysmenorrhea	2 (0.4 per cent)
Functional amenorrhea	2 (0.4 per cent)

It is found in both functional uterine bleeding and functional amenorrhea, which suggests that it is not an important factor in either of these conditions. Approximately half of the specimens of premenopausal hyperplasia were obtained from patients with functional bleeding. The low incidence of functional amenorrhea with hyperplasia as shown in this study is a false estimate of its occurrence, because we have examined the endometria in so few cases of amenorrhea. However, in the light of our present knowledge that amenorrhea is not always due to quantitative ovarian deficiency, we believe that the performance of

*Read, by invitation, at the Sixty-Second Annual Meeting of the American Gynecological Society, held at Swampscott, Mass., May 31 to June 2, 1937.

year it had become metrorrhagia. She was then referred to my department, the uterus being then the size of a three and one-half months' pregnancy. The diagnostic curettage showed the so-called fish flesh material which is so diagnostic of sarcoma.

This patient had had her metastatic tumor identified before the primary. I want to emphasize that a woman at any age who has a tumor in her chest should be examined for the possibility of a primary tumor in the uterus, and when a sarcoma is found in the uterus it should also be looked for in the lung.

As to treatment with radiation, we have not cured a single case of sarcoma of the uterus with radiation.

DR. CAREY CULBERTSON, CHICAGO, ILL.—In the last two years I have had two cases of sarcoma of the uterus. The first one was a sarcoma botryoides combined with an adenocarcinoma in the fundus. The second case, an obese Bohemian woman, was operated upon with a provisional diagnosis of uterine fibroma. On opening the tumor after its removal it was seen that the growth was diffuse, not encapsulated. The surgical pathologist made a diagnosis of sarcoma of the so-called degenerative fibroid type.

That brings up the question as to whether these tumors are sarcomatous originally, or whether they are fibroids that have become sarcomatous, a theory I do not hold to strongly. This patient had no symptoms, had passed her menopause, had no leucorrhœa, no bleeding, no pain and had not lost weight.

These two cases illustrate the differences that both Dr. Novak and Dr. Healy have referred to. We expect the second patient to get well. The first patient died within about fifteen months with metastases.

DR. KARL M. WILSON, ROCHESTER, N. Y.—Dr. Novak referred to a patient from whom I sent him a specimen for diagnosis. The patient was entirely unsuitable for surgery and she was treated only by radiation therapy. She got along very well for a year with no symptoms but now is on a rapid down hill course.

One other patient I have seen during the past year, was interesting because one-half of a myoma was solid calcification, the other was rapidly growing sarcoma. This patient also went rapidly down hill after her operation.

DR. NOVAK (closing).—As regards the incidence of sarcomatous degeneration of myomas, there would seem to be no doubt that the wide discrepancies to be found on this point are explainable by individual differences in the histologic criteria of sarcoma. The common error, especially in the earlier literature, was to mistake very cellular but perfectly benign myoma for sarcoma. Even now there is a residuum of cases in which pathologists will disagree, just as they do in the diagnosis of early carcinoma, because of similar differences of opinion as to criteria. Generally speaking, even a very cellular tumor should not be called sarcoma if the constituent cells exhibit striking uniformity and a complete absence of anaplastic activity. When, on the other hand, there is marked disparity of both nuclei and cytoplasm, with hyperchromatosis, possibly giant cells, and often mitoses, no other histologic diagnosis seems possible. The finding of mitoses in the individual section is not essential for diagnosis, but as a rule they are present, and we believe their number gives at least an approximate idea of the degree of malignancy of the tumor.

One of the sections I threw on the screen showed an unusually rich distribution of mitotic figures. It came from a private patient of my own who came under observation after almost exsanguinating bleeding. A diagnostic curettage done after transfusion established the diagnosis of sarcoma. Under radiotherapy and further transfusion her general condition improved so strikingly that a radical operation was carried out with excellent immediate result, but with rapid recurrence, metastases and death six or seven months later. In one of our patients metastasis occurred to the heart muscle and a similar case, in which I had the opportunity of studying sections, has been reported by Dr. Criscitiello, of Pittsfield.

blood and urine studies revealed evidence of persistent hyperestrinism throughout the five weeks of observation.

Evidence that hyperplasia and long periods of amenorrhea are compatible is seen in Fig. 3, from a patient thirty-four years of age who had not menstruated for eight years. A week following the curettage,



Fig. 2.—(Gyn. Path. No. 18,008. $\times 154$.) Hyperplasia with oligomenorrhea. Patient aged twenty-four years. Irregular scanty periods for two years. Last period four months ago.



Fig. 3.—(Gyn. Path. No. 16,328. $\times 115$.) Hyperplasia with amenorrhea. Patient aged thirty-four years. No period for eight years.

profuse uterine bleeding occurred. While amenorrhea with hyperplasia probably is a common occurrence, determination of its actual incidence must await a large series of endometrial biopsies.

On the other hand, abundant information is available concerning the incidence of hyperplasia in functional bleeding, uterine myomas, endometriosis and various adnexal lesions, as is shown in Table II. In this

endometrial biopsies in this condition will disclose many more instances of its association with hyperplasia.

Next to functional bleeding the greatest number of hyperplasias occurred in combination with uncomplicated uterine fibroids, 29.5 per cent of the total. The third highest number of hyperplasias appeared in association with relaxation of the pelvic floor, which accounted for 36 (7.3 per cent) of the total number. Most of these patients had experienced no menstrual abnormalities, but were subjected to diagnostic curettage prior to plastic procedures. Eight (1.6 per cent) of the hyperplasias were associated with fundal malignancy and one with cervical carcinoma. The wide distribution of hyperplasia herein shown arouses the suspicion that it is a coincidental occurrence rather than a symptom-producing entity.

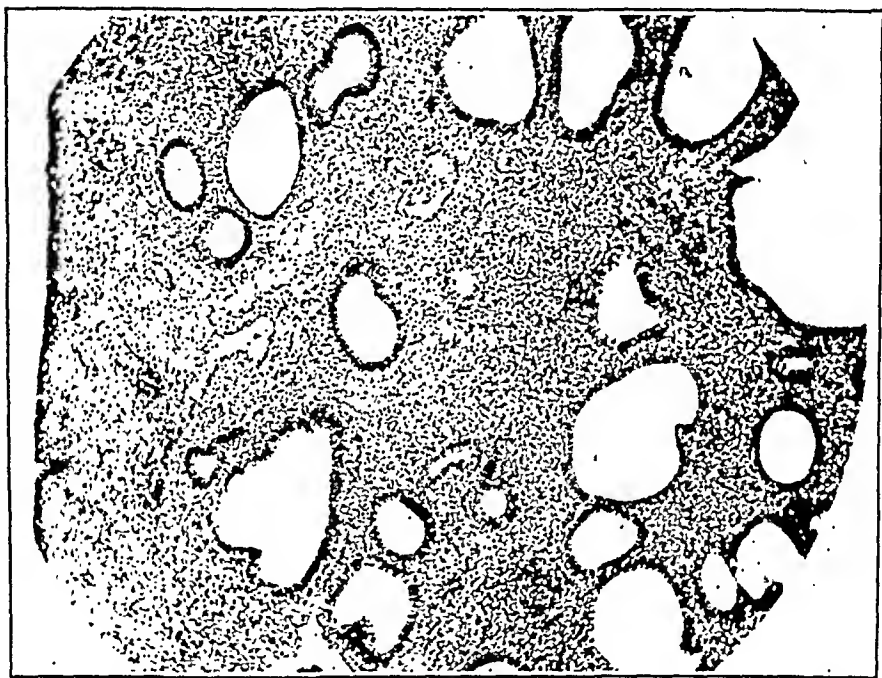


Fig. 1.—(Gyn. Path. No. 10,909. $\times 90$.) Typical hyperplasia. Patient aged fourteen years. Continuous bleeding from onset of menstruation, at eleven years, until this curettage.

The frequent association of hyperplasia with functional bleeding has led to the belief that one is a necessary adjunct to the other. A typical example of this association is seen in Fig. 1. This specimen was obtained from a child of fourteen years whose menstruation began at eleven and continued without interruption until the curettage was done. All of the characteristic features of hyperplasia are seen in this section. A similar picture is shown in Fig. 2 from a patient twenty-four years of age with oligomenorrhea who, after a year's amenorrhea, had spotted at irregular intervals for nine months, but had experienced no bleeding for the last four months. Four other biopsy specimens were collected at weekly intervals and all showed hyperplasia. Simultaneous

has been suggested, and Hoffbauer has reported overgrowth of the basal endometrial layer in castrate animals following injections of anterior lobe extracts. The microscopic similarity between hyperplasia and the active basal layer lends support to the possibility that both are controlled by the same hormonal influence, which may arise in the hypophysis. Acceptance of this theory would explain postmenopausal hyperplasia.

The dual occurrence of hyperplasia and abnormal uterine bleeding has been recognized since this endometrial change was first described. Witherspoon states that "endometrial hyperplasia is characterized by profuse and irregular bleeding from the uterine." Fluhmann found the outstanding symptom of hyperplasia to be abnormal uterine bleeding. Graves emphasized the almost universal presence of gland dysplasia in arrhythmic dysfunctional bleeding. The opposite opinion is voiced by Kmzrok and Wilson, who state that "functional bleeding is completely independent of the type of endometrium." The present study indicates that abnormal bleeding is not a necessary accompaniment to endometrial hyperplasia, and that hyperplasia is not an essential adjunct to dysfunctional bleeding.

Discussion of the types of bleeding in this paper includes the term "abnormal" to mean menorrhagia, metrorrhagia, menometrorrhagia, or polymenorrhea. The term "normal" designates bleeding at regular intervals, of the average duration and amount with no recent change in its characteristics. We realize that such bleeding from a hyperplastic endometrium is not normal menstruation in the strict physiologic sense. "Oligomenorrhea" in this discussion denotes scanty periods, either as to interval, amount or duration, including all instances of temporary cessation of periods up to four months. After that time the term "amenorrhea" is applied.

The clinical records of 487 patients with endometrial hyperplasia show that abnormal bleeding occurred in 85.2 per cent and normal, scanty, or absent periods in 14.8 per cent (Table III). Of the latter

TABLE III. PREMENOPAUSAL HYPERPLASIA, RELATIONSHIP OF AGE TO ABNORMAL BLEEDING

(Exclusive of Nine Cases Associated With Uterine Malignancy)

AGE	NUMBER	ABNORMAL PER CENT	NORMAL PER CENT	OLIGOMEN- ORRHEA PER CENT	AMENOR- RHEA PER CENT
10-19	14	100.0	0.0	0.0	0.0
20-29	42	80.0	17.0	0.0	3.0
30-39	121	79.0	16.5	3.6	0.9
40-49	253	86.5	11.1	1.9	0.5
50-59	57	94.5	1.7	1.8	1.8
Total number		487			
		Abnormal bleeding		415 (85.2%)	
		Normal, scanty or absent periods		72 (14.8%)	

TABLE II. PREMENOPAUSAL HYPERPLASIA, INCIDENCE IN ITS COMMONLY ASSOCIATED CONDITIONS

	NUMBER OF ENDOMET. SPECIMENS	PERCENTAGE OF HYPERPLASIA
Functional bleeding	676	35.8
Myoma uteri	750	19.4
Myoma and endometriosis	84	9.5
Myoma and ovarian cyst	31	32.2
Myoma and pelvic inflammatory disease	152	7.2
Endometriosis	55	10.9
Pelvic inflammatory disease	101	10.9
Ovarian cyst	30	43.3
Total number of endometrial specimens, 1,879		
Total number of hyperplasias, 447 (24.0 per cent)		

series, the endometrial sections from 676 patients with functional bleeding showed hyperplasia in 35.8 per cent. These figures confirm the opinion of both myself and others that endometrial hyperplasia is not a necessary, nor even an usual, accompaniment to abnormal bleeding of functional origin.

The frequent association between hyperplasia and uterine myomas has been emphasized by numerous authors, who found the following incidence: Witherspoon, 40 hyperplasias in 44 myomas; King, 71 per cent in 114 cases; Kanter and Klawans, 53 per cent in 100 uteri; and E. M. Blair, 80 per cent in 83 specimens. The incidence of hyperplasia in our series did not approach these figures. Of 750 uncomplicated myomas, hyperplasia was found in 146 (19.4 per cent). By adding to these the tumors complicated by adnexal lesions a total of 1,017 is obtained, 17 per cent of which had associated hyperplasia. Such a low incidence of hyperplasia in association with myomas does not indicate a common etiology for the two conditions.

Witherspoon suggests that endometriosis and endometrial hyperplasia may result from a common stimulus. The occurrence of 10.9 per cent of hyperplasia in 55 cases of endometriosis in the present series does not support his theory.

Except for functional bleeding, the highest incidence of hyperplasia accompanied ovarian cysts (43.3 per cent). By including the uncomplicated cysts with those associated with myomas, 23 specimens were available. Five of these were neoplastic and 18 were retention cysts of the follicular type. The common association of hyperplasia and follicular cysts of the ovary is generally recognized. On the other hand, hyperplasia may occur with normal ovaries containing active corpora lutea, as was pointed out by Novak and Martzloff. Recently, we found hyperplasia along with a typical corpus luteum cyst. This occurrence casts doubt upon the commonly accepted opinion that hyperplasia always results from unbridled follicular stimulation in the absence of the luteal hormone. Possible direct influence by the anterior lobe secretion

pliated ovarian cysts with hyperplasia. By combining these with the cysts complicated by myomas to make a total of 23, a 61 per cent incidence of menstrual aberrations is noted (Table V). Eighteen of the

TABLE IV. PREMENOPAUSAL HYPERPLASIA, INCIDENCE OF ABNORMAL BLEEDING IN ITS ASSOCIATED CONDITIONS—447 CASES

	ABNORMAL PER CENT
Functional bleeding	100
Myoma uteri	89
Myoma and endometriosis	50
Myoma and ovarian cyst	50
Myoma and pelvic inflammatory disease	82
Endometriosis	83
Pelvic inflammatory disease	45
Ovarian cyst	70

TABLE V. PREMENOPAUSAL HYPERPLASIA, RELATION OF ASSOCIATED OVARIAN CYSTS TO THE CHARACTER OF BLEEDING—TOTAL NUMBER, 23

Retention cysts	18	Abnormal bleeding	13 (72 per cent)
Neoplastic cysts	5	Abnormal bleeding	1 (20 per cent)
Total with abnormal bleeding 14 (61 per cent)			

23 were retention cysts and excessive bleeding accompanied 13 (75 per cent). Of the five neoplastic cysts, menstrual disturbances occurred in only one (20 per cent). These figures suggest the possibility of a mutual background for the development of the retention cysts of the ovary and for the occurrence of irregular uterine bleeding.

POSTMENOPAUSAL HYPERPLASIA

Postmenopausal hyperplasia is found both in the presence and in the absence of demonstrable pelvic pathology. Frequently it is not accompanied by uterine bleeding. In this study, no patient was considered to be postmenopausal unless she had reached the menopausal age and had gone a year without uterine bleeding. There were 38 such patients, ranging from one to twenty-three years after the menopause.

That postmenopausal hyperplasia occurs in a wide variety of pelvic conditions is shown in Table VI. Unlike premenopausal hyperplasia, a

TABLE VI. POSTMENOPAUSAL HYPERPLASIA, DISTRIBUTION OF 38 SPECIMENS

Ovarian carcinoma	4 (11 per cent)
Granulosa cell carcinoma	2 (5 per cent)
Fundal carcinoma	4 (11 per cent)
Cervical carcinoma	1 (2 per cent)
Pelvic floor relaxation	3 (8 per cent)
Ovarian cyst—benign	3 (8 per cent)
Myoma uteri	8 (21 per cent)
Unexplained uterine bleeding	13 (34 per cent)

high incidence of associated malignancy is noted, 11 (29 per cent) of the 38 cases in this group. Of the benign lesions, the most frequent to

group of 72 patients, 56 had normal periods, 10 had oligomenorrhea, and 6 were amenorrheic for intervals of four months to eight years. Two cases of amenorrhea were functional, and one occurred with each of the following conditions: Pelvic inflammatory disease, uterine desecens, paraovarian cyst and myoma uteri. This list is fairly representative of the conditions in which hyperplasia and abnormal bleeding are usually found, yet these amenorrheic patients lacked something to stimulate, or possessed something to prohibit, uterine bleeding.

So far as age is concerned, the incidence of abnormal periods is seen to be about equal from the third to the fifth decade of life, with a sharp increase after this age suggesting the occurrence of some hormonal change after forty years of age which increases the tendency to bleed. In this series, the high incidence of flooding with hyperplasia in the second decade is expected for, with rare exceptions, abnormal bleeding



Fig. 4.—(Gyn. Path. No. 10,821, $\times 130$.) Hyperplasia with regular periods. Patient aged forty-four years. Last period ceased eight days before this curettage.

was the only indication for curettage. From the third to the fifth decade, normal periods frequently accompany endometrial hyperplasia. An example of this is seen in Fig. 4 which shows the endometrium of a patient, forty-four years old, upon whom a repair was performed. Her menstrual periods had always been normal, the last having ceased eight days before the curettage. The normal proliferative phase has been replaced by typical endometrial hyperplasia.

Further evidence of the diversity between the incidence of hyperplasia and of abnormal bleeding is seen in Table IV. A marked variation in the frequency of menstrual irregularities occurred, despite the presence of endometrial hyperplasia in all of the specimens. The most striking difference is the 89 per cent incidence of irregular bleeding in myoma with hyperplasia against 45 per cent in pelvic inflammatory disease. Abnormal bleeding was present in 70 per cent of the uncom-

shows typical hyperplasia from a patient who was operated upon six years after her menopause for a pseudomucinous cyst of the ovary.

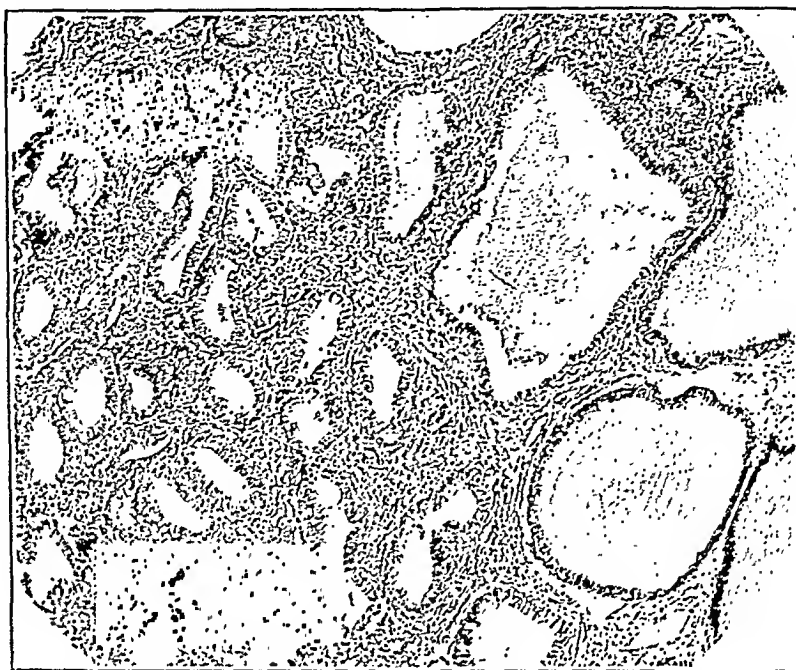


Fig. 6.—(Gyn. Path. No. 13,154. $\times 90$.) Postmenopausal hyperplasia with bleeding. Patient aged sixty years. Menopause at forty-nine years. Bleeding for eight days, as free as a period.



Fig. 7.—(Gyn. Path. No. 19,392. $\times 90$.) Postmenopausal hyperplasia with bleeding. Patient aged sixty-six years. Menopause at fifty-nine years. Scant irregular bleeding for a month.

There had been no bleeding since the menopause. Just why that patient should not bleed, and both of the patients of the following specimens should do so, cannot be explained.

be associated with postmenopausal hyperplasia was the myoma (21 per cent). No pelvic pathology, except the endometrial hyperplasia, was found in one-third of the patients, all of whom were curetted because of postmenopausal bleeding. Of the 13 patients in this group, the intervals between the menopause and the onset of symptoms were two to five years, 2 patients; five to ten years, 3 patients; ten to twenty years, 6 patients; twenty to twenty-three years, 2 patients.

The occurrence of hyperplasia at this age has not been explained satisfactorily.

Taylor suggested that it may be the remains of premenopausal hyperplasia, but it is difficult to comprehend why the endometrium should not accompany the other pelvic structures in their atrophic changes. Novak has made two suggestions, pos-

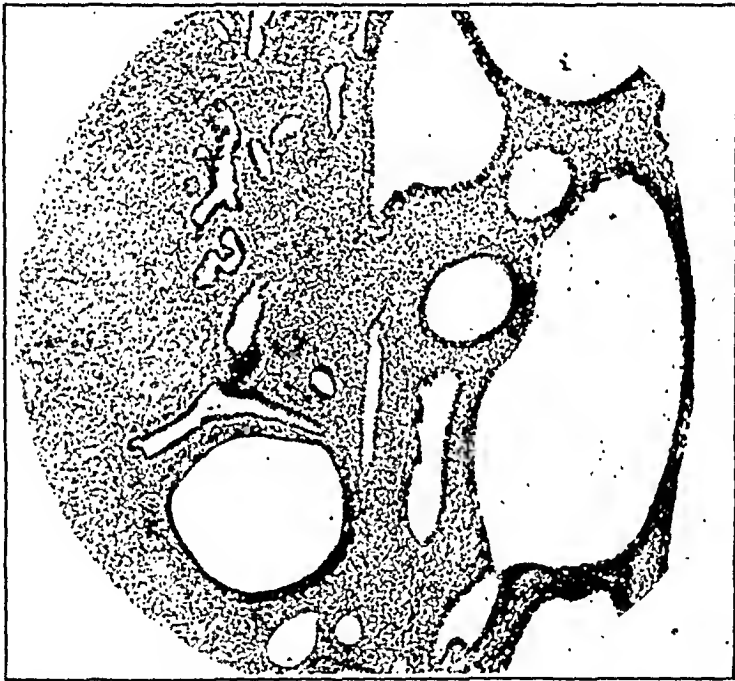


Fig. 5.—(Gyn. Path. No. 17,753. $\times 74$.) Postmenopausal hyperplasia. Patient aged fifty-five years. Menopause at forty-nine years. No bleeding since.

sible postmenopausal continuance of estrin production by the ovaries and the possibility that the anterior pituitary lobe may assume estrogenic function after the menopause. The latter theory is supported by the report by Frank and Goldberger of the urinary excretion of the estrogenic factor by 12 surgical castrates. Hoffbauer's stimulation of the basal endometrium in castrates with anterior pituitary extracts suggests that postmenopausal hyperplasia may arise from anterior lobe stimulation.

While this problem is still in the realm of conjecture, it is no more uncertain than the explanation of postmenopausal uterine bleeding in the absence of accountable pelvic pathology. Evidence that hyperplasia *per se* does not cause the bleeding is seen in the fact that 11 of the 33 patients with postmenopausal hyperplasia had not bled since the menopause (Table VII). The conditions which obviously cause bleeding, cervical and fundal malignancy, are excluded from this table. Fig. 5

HYPERPLASIA AND FUNDAL CARCINOMA

The relationship between endometrial hyperplasia and fundal carcinoma has been the subject of considerable discussion. We have not started with the fundal malignancies and searched for hyperplasia, as Novak did, but we have searched for malignancy in the specimens of hyperplasia, with the following results. Of 2,070 endometrial specimens, hyperplasia was found in 534 (25.8 per cent). Thirteen (2.4 per cent) of the hyperplasias were associated with fundal carcinoma (Table IX). If hyperplasia predisposes to carcinoma the incidence of malignancy should exceed the 2.4 per cent herein recorded.

By dividing the specimens into pre- and postmenopausal groups we found associated malignancy in 1.8 per cent of the first, and 10.5 per cent of the latter, showing the frequency of postmenopausal hyperplasia



Fig. 8.—(Gyn. Path. No. 16,079. $\times 90$.) Postmenopausal hyperplasia with superimposed adenocarcinoma.

TABLE IX. ENDOMETRIAL HYPERPLASIA, INCIDENCE OF FUNDAL CARCINOMA

Number of endometrial specimens	2,070
Number with hyperplasia	534 (25.8%)
Superimposed carcinoma	13 (2.4%)
Premenopausal hyperplasia	496
Superimposed carcinoma	9 (1.8%)
Postmenopausal hyperplasia	38
Superimposed carcinoma	4 (10.5%)

with carcinoma to be 5.8 times that of the premenopause. This figure is less significant when we are reminded that the usual incidence of postmenopausal fundal malignancy is 3 to 4 times that of the premenopausal era. Two hundred forty-one specimens of fundal malignancy in our laboratory are divided into premenopausal 54 and postmenopausal 187, the latter being 3.3 times as frequent as the former.

Fig. 6 was obtained from a patient whose bleeding occurred eleven years post-menopausally. At the time of the curettage, the endometrial tissue was benign. She was given 600 mg. hr. of intrauterine radium, with no recurrence of symptoms. Fig. 7 was recovered seven years after the menopause. The curettings were benign and 1,200 mg. hr. of radium were administered with no subsequent bleeding.

TABLE VII. POSTMENOPAUSAL HYPERPLASIA, INCIDENCE OF BLEEDING—33 PATIENTS
(Cases of Associated Uterine Malignancy Excluded)

	BLEEDING	NO BLEEDING
Myoma uteri	6	2
Ovarian cyst, benign	0	3
Ovarian carcinoma	1	3
Granulosa cell carcinoma	1	1
Pelvic floor relaxation	1	2
Unexplained bleeding	13	0
	22	11
	(66.6 per cent)	(33.3 per cent)

TABLE VIII. POSTMENOPAUSAL HYPERPLASIA, TREATMENT

Hysterectomy and bilateral salpingo-oophorectomy	20
Dilatation and curettage	5
Dilatation and curettage and intrauterine radium, 600 mg. hr.	3
Dilatation and curettage and intrauterine radium, 1,200 mg. hr.	5
Dilatation and curettage and intrauterine radium, 2,400 mg. hr.	4
Dilatation and curettage and intrauterine radium, 3,600 mg. hr.	1

Table VIII shows the treatment of the 38 patients with postmenopausal hyperplasia. Of the 18 who were not treated by hysterectomy, 4 had myomas, 2 relaxation of the pelvic floor, and 12 unexplained uterine bleeding. A simple curettage was done for 5 and for the remainder, curettage and intrauterine radium of the dosage indicated. Those who received 2,400 to 3,600 mg. hr. of radium had curettings which were so suggestive of malignancy that it was only after careful microscopic study that this diagnosis was disproved. The remainder were apparently benign at the time of the curettage, and microscopic study verified this opinion. Of the 18 patients, 4 were treated from one to two years ago, 5 from four to six years ago, and 9 from six to twelve years ago. Seventeen had no recurrence of symptoms and one reported the return of spotting six years after a curettage and 1,200 mg. hr. of radium. A second curettage revealed nothing malignant and four years have elapsed with no further symptoms. That the hyperplasia occurred in this group of patients without associated ovarian neoplasm is proved by the facts that no adnexal pathology was demonstrable at the original examination and that the bleeding has not recurred up to the present time. The absence of bleeding for intervals ranging from one to twelve years also warrants the assumption that in no instance has malignancy been engrafted upon the hyperplasia.

months of amenorrhea. In another slide (Fig. 9B), cut from the same block, the area of carcinoma was found. That this occurrence is not limited to older patients is evidenced by the fact that 3 of the 9 patients with premenopausal hyperplasia with carcinoma were less than forty years of age. (Gross examination of the curettings may be misleading, for it enabled the diagnosis of malignancy in only 5 of the group. In the other 4 the characteristic macroscopic appearance of hyperplasia prevailed, and it was only upon microscopic study that the carcinoma was detected.

SUMMARY AND CONCLUSIONS

The clinical records of 534 patients with endometrial hyperplasia have been analyzed in the effort to determine its rôle in benign uterine hemorrhage, both before and after the menopause, and to evaluate the significance of its association with myomas, endometriosis and fundal carcinoma.

The presence of hyperplasia usually implies abnormal bleeding, but this is not a constant occurrence for such bleeding accompanied only 85 per cent of the premenopausal hyperplasias in this study. The remainder were attended by normal periods, oligomenorrhea or amenorrhea. When hyperplasia was found to be associated with other pelvic lesions, the frequency of abnormal bleeding varied according to the type of complicating lesion. Of the myomas with hyperplasia, 89 per cent had irregular periods, against 70 per cent of the ovarian cysts and 45 per cent of the cases of pelvic inflammatory disease. Such variation, despite the constant presence of hyperplasia, suggests that some influence other than the endometrial change precipitated the pathologic bleeding. Further evidence that hyperplasia does not necessitate abnormal bleeding is noted in the fact that one-third of the patients with postmenopausal hyperplasia had experienced no bleeding since the menopause. Just as hyperplasia may occur without abnormal bleeding, so may abnormal bleeding occur without hyperplasia. Approximately two-thirds of the cases of functional uterine hemorrhage in the present series yielded endometria which were devoid of hyperplasia.

The significance of the association between hyperplasia and benign pelvic lesions, as myomas, endometriosis, pelvic inflammatory disease and ovarian cysts, is uncertain. The theory that myomas and hyperplasia have a common etiologic basis loses support by the occurrence of hyperplasia in only 17 per cent of the myomatous uteri in this study. If the two conditions are allied in origin, the 496 specimens of hyperplasia should have been accompanied by myomas more frequently than one out of three times, as occurred in this series. The absence of myomas in 65 per cent of the hyperplasias and the absence of hyperplasia in 83 per cent of the myomas suggests different origins for the two conditions.

While malignancy occasionally accompanies hyperplasia, the clinical importance of this association depends less upon the predisposition of hyperplasia to the development of carcinoma, than upon the possibility that an obscure area of malignancy may be overlooked, or may not be sectioned, in an endometrial specimen which is dominated by hyper-



Fig. 9A.—(Gyn. Path. No. 16,598 $\times 95$.) Typical hyperplasia. Patient aged forty-eight years. Irregular bleeding for three months, after eight months amenorrhea.



Fig. 9B.—(Gyn. Path. No. 16,598. $\times 135$.) Hyperplasia with superimposed carcinoma.

plastic changes. Such an error would seem impossible in the light of Fig. 8, showing postmenopausal hyperplasia in juxtaposition to obvious carcinoma. Fig. 9, however, depicts a different situation and demonstrates the value of multiple sections from endometrial curettings. First (Fig. 9A), is the typical hyperplasia recovered from a patient forty-eight years old, with irregular bleeding for three months, following eight

also been noted by Schroeder and was noted by Novak and Martzloff in 16.9 per cent of their material. However, I do not believe that in the case of the thirty-year-old patient, mentioned by Dr. Payne, who had not menstruated for eight years, that one should infer that this patient's endometrium was hyperplastic during this entire period, or that one may reasonably assume an apparently causative hyperestrinemia to have existed during the preceding eight-year interval.

Dr. Payne has observed also that in 56 (11.4 per cent) of his patients there was a history of normal menstruation in the presence of hyperplasia. In fact, 36 (7.3 per cent) of his specimens represented routine curettings obtained from patients about to undergo reparative operations on the birth canal. This corresponds closely to a similar group of patients, reported from Cullen's clinic, who also gave a history of normal menstruation. It is worth noting, however, that these figures, just as Dr. Payne's, are based on histories generally obtained by others from ward patients who, at times, are very unobservant of menstrual abnormality.

The question of the histologic criteria used by individual investigators in recognizing hyperplasia is of fundamental importance. If moderate variations in the size of endometrial glands are to be interpreted as abnormalities then one is plunged immediately into confusion. For, after all, the normal variation that occurs in gland shape, luminal diameter and tinctorial reaction in various fields and even in a single low power field of the zona compacta and spongiosum of a normal endometrium may be marked. This occurs whether the endometrium is a menstruating one, as shown so well by Bartelmez and Culbertson, or whether it is in the preovulatory or post-ovulatory phase of the intermenstruum.

This uneven response of similar layers of the endometrium to an apparently uniform hormonal stimulus, while probably not generally appreciated, nevertheless has been known for years. It probably indicates that the endometrium, as an end organ, so to speak, for the action of the ovarian hormones, must vary in its receptivity to a given hormonal stimulus.

Normal uterine glands during the various phases of the intermenstruum may vary from about 16 to 160 microns in their short diameters. A difference in the gland diameters of 30 to 80 microns in the same microscopic field of normal endometrium where the diameters ordinarily are less than 160 microns, is a common observation.

It would be helpful if one could reduce the most spectacular phase of hyperplasia endometrii to a mathematical formula, for difference in gland size along with large glands is one of its arresting and most easily recognized characteristics. In unmistakable preparations the differences between maximum and minimum diameters in a single field are generally greater than 150 microns. However, if the gland diameters in a given area are all over 250 microns, obviously variations are no longer diagnostically significant for the glands are all abnormally enlarged.

The section shown by Dr. Payne as an example of typical hyperplasia from a woman with a normal menstrual history impresses me more as that of a normally developing endometrium probably reflecting a late preovulatory or an early postovulatory or progestin response and showing also the picture of uneven development or so-called irregular ripening. If my surmise is correct that these endometria represent merely normal variations, it will help explain the large number of so-called hyperplastic endometriums obtained by Dr. Payne from women with normal menstrual histories.

The extremely dilated glands, measuring 800 to 1,000 microns in diameter which are lined by flattened epithelium and occur in some postmenopausal or occasional amenorrheic endometria, are I believe controversial. To accept them as unequivocal evidence of an active or pre-existing hyperplasia is probably debatable, if other supportive evidences of hyperplasia such as large glands lined by columnar epithelium, mitoses, etc., are lacking.

The incidence of hyperplasia in association with endometriosis was the same as that found in pelvic inflammatory disease (10.9 per cent.), while 43 per cent of the ovarian cysts were accompanied by hyperplasia. We consider hyperplasia in these conditions to be the endometrial response to disturbed ovarian function and hope that the unusually high incidence of hyperplasia in ovarian cysts will be explained by hormone studies upon the cyst fluid, which we are now in the process of making.

The existence of certain points of similarity between the microscopic appearance of marked hyperplasia and of fundal malignancy is generally conceded. While the stimulative processes which produce hyperplasia theoretically might continue until the endometrium assumes malignant characteristics, the 2.4 per cent incidence of hyperplasia with superimposed carcinoma in this study indicates that, if this excessive stimulation does occur, it must do so with extreme rarity. It has been suggested postmenopausal hyperplasia particularly favors the development of carcinoma. Its occurrence in this series, 5 times more often than in the premenopause, would seem to support the suggestion, except that postmenopausal fundal carcinoma is generally conceded to be 3 to 4 times as common as premenopausal, regardless of the type of the associated endometrium. The significance of the association between hyperplasia and fundal malignancy seems to lie more in the danger that the hyperplasia may so dominate the pathologic picture as to obscure the malignant change than in the likelihood that it will favor the development of carcinoma.

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133 SOUTH THIRTY-SIXTH STREET

DISCUSSION

DR. KARL H. MARTZLOFF, PORTLAND ORE.—Hyperplasia endometrii twelve to fifteen years ago was a term employed in only a few laboratories. Now, however, the pendulum has swung so far that one sees the term hyperplasia endometrii applied to virtually any interval type of endometrium associated with abnormal uterine bleeding. Certainly if this term is used its use should be restricted to the characteristic process to which it was first applied by Cullen and to which it has been restricted by Novak, Schroeder, TeLinde, Fluhmann, and others.

The occurrence of hyperplasia endometrii in the presence of amenorrhea, or more commonly with a history of amenorrhea preceding the bleeding phase, is also not generally appreciated and has been clearly reemphasized by Dr. Payne as occurring in 6 per cent of the University of Pennsylvania material. This phenomenon has

hormone levels, just as the urinary spill of sugar may occur at different blood sugar levels. This viewpoint I have already presented in the discussion of Dr. Ross' paper.

The diagnosis of hyperplasia should, therefore, be reserved for the cases in which there is a greater or less degree of proliferation of the endometrial elements, though it is difficult to draw hard and fast rules as to where normal proliferation ends and where the abnormal begins. In the common type of functional bleeding the underlying cause is a failure of ovulation, with a persistence of estrone effect, and an absence of the corpus luteum hormone and its effects. In the much smaller group of functional bleeding cases in which a secretory endometrium is found, the mechanism is different, though the bleeding may be just as truly functional. Hyperplasia represents simply a maximum growth effect, and nothing seems more clearly established than that the growth effects of estrone do not necessarily parallel the bleeding propensities of the endometrium. The factor which seems far more important in bringing about the bleeding spill is the quantitative hormonal interreaction of the hypophysis and the ovaries.

I do not believe there is any worthwhile evidence to associate myoma and hyperplasia casually, especially in view of the fact that myoma occurs also in many other organs and tissues in which a hormonal relation is difficult to conceive of. There is much more reason, it seems to me, to associate hyperplasia, which is an endometrial overgrowth, with uterine adenomyosis, which is a similar endometrial overgrowth carried to the point of invasion of the musculature, plus a striking overgrowth of the latter.

I agree with Dr. Payne that no evidence exists to indicate that the common type of hyperplasia seen during reproductive life predisposes to adenocarcinoma, but I do believe that an important relation of some sort exists between postmenopausal hyperplasia and adenocarcinoma on the basis of evidence from our laboratory which I presented before this Society last year. I cannot review this here, but I may say that we have during the past year encountered quite a group of cases again illustrating this relationship, and are more than ever convinced of its possible importance.

DR. C. FREDERIC FLUHMAN, SAN FRANCISCO, CALIF.—Early studies of hyperplasia were based solely on the histologic picture of the endometrium and many speculations were made as to the etiology of the condition. More recent work has served to show that it is the manifestation of an endocrinologic disturbance, and it has been possible to reproduce it in both experimental animals and in castrate women. There can scarcely be any question that it is bound up with the action of estrogenic hormones which are either manufactured or possibly merely changed and utilized by the ovaries. These substances are known to be stimulants to endometrial growth, and under conditions as yet not too well understood, they may result in the intense overgrowth of the uterine mucosa which we know as hyperplasia. I can find no necessity for attributing this additional quality to the many virtues of the anterior hypophysis, especially since this concept is based on incomplete experimental work performed with another species and as yet unconfirmed.

It thus seems established that hyperplasia results from a stimulation by estrogenic hormones, in the absence of a corpus luteum influence—and not necessarily by a hyperestrinism but even by a prolonged constant stimulation of small amounts of the hormone. On the other hand, it is difficult at the present to explain the occurrence of bleeding in such cases. Uterine hemorrhage may occur as a persistent metrorrhagia, as a type of cyclic bleeding such as is found in the anovulatory cycles of monkeys, and this endometrial picture is often noted in patients with longer or shorter periods of amenorrhea. It is futile to speculate at present on the actual mechanism of the hemorrhage, and I fail to see how an explanation can be given be-

Histologic study of these endometria may be of some prognostic value in the premenopausal group. If, for example, the endometrium shows a bona fide widespread hyperplasia, the outlook for the correction of the underlying glandular dysfunction and the reestablishment of a normal menstrual cycle by conservative measures is, I believe, relatively poor. Contrariwise, if isolated and infrequent areas of hyperplasia occur in an endometrium that in most areas shows its apparent ability to respond normally to hormonal stimuli, then the outlook for recovery without resorting to radiation or hysterectomy is appreciably better.

DR. CAREY CULBERTSON, CHICAGO, ILL.—One thing is usually left out in discussions of the factors behind hyperplasia. That is the question of multiparity. Special consideration should be given the regeneration of the endometrium following labor or abortion. Regeneration is never 100 per cent perfect any more than involution is 100 per cent perfect in the uterine mucosa.

The first section shown in the slides is not a hyperplasia. It is what would be called a normal endometrium, but the woman has had 8 children. She is forty-four years of age and was bleeding excessively, hypermenorrhea of the menorrhagic type.

This section, which represents the general condition throughout the whole endometrium, resembles a benign adenoma, with little or no stroma. Now it is the stroma that is required for the production of decidua and the reception of a fertilized egg, and it seems to me to be of first importance in considering the significance of a given endometrial pattern.

This second slide shows the ordinary hyperplasia or irregularity of the glands. It is about two times as thick as the normal endometrium.

The third shows a hyperplasia in a young woman with an abundance of stroma. It is in the pregravid stage and resembles very much the decidua of pregnancy. One might easily mistake these glands for the "glands of pregnancy" that we are all familiar with.

In the next slide is shown the hyperplasia of the Swiss-cheese type. There are markedly dilated glands but still there is enough stroma left. This woman had borne only one child.

The fifth slide is from a woman forty-two years of age who had had 9 children and two abortions. Longitudinal and cross-section of this tissue shows an almost entire absence of stroma. This is, however, a hyperplasia, the endometrium being about three times as thick as normal.

All of this brings up problems relative to endometrial regeneration and the stimulus involved. It would appear that the epithelial elements regenerate better than the stroma, when this regeneration takes place repeatedly.

DR. EMIL NOVAK, BALTIMORE, MD.—Constant reference is made to the confusion in the microscopic diagnosis of hyperplasia, and this confusion unquestionably exists. The reason for this lies in the fact that at one time we all believed that the characteristic endometrial finding in cases of functional bleeding was that of typical hyperplasia, and the tendency has been to fit the microscopic diagnosis to the clinical diagnosis of functional bleeding.

We have long since in our own laboratory ceased to make such labored diagnoses, for it has become clear that functional bleeding may occur not only from an endometrium of the typical Swiss-cheese pattern, but also from one of the normal interval or secretory type, or even from an atrophic mucosa. The same statement can be made with reference to amenorrhea. Unless one invokes some unknown special bleeding factor, the evidence for which is rapidly dwindling, such observations point clearly to the fact that the "bleeding level" of the endometrium exhibits marked individual variations, and that the spill of blood may occur at different

OBSERVATIONS PERTINENT TO GONADOTROPIC THERAPY IN GYNECOLOGY*

ROBERT A. ROSS, M.D., F.A.C.S., DURHAM, N. C.

(From the Department of Obstetrics and Gynecology, Duke University Hospital)

FOR the past seven years we have studied ovaries and endometriums of patients who had received injections of various gonadotropic principles. We were concerned originally with the possibility that some of the responses observed in animals might occur in the human being. Later we have tried to explain the reported instances of clinical improvement without significant histologic changes. Recent studies have been concerned primarily with responses in the anovulatory states. An attempt to employ the endometrium as an indicator of the levels of ovarian function has resulted in an alteration of our classification of endometrial patterns. These studies have suggested, in addition, an avenue which may help ascertain the required clinical dose of these preparations. Attempts at therapy are influenced by various factors which may include the age of the patient, and associated pelvic conditions as well as individual receptivity.

The term "gonadotropic principle" designates certain substances that have characteristic effects on the gonads of test animals. There is no identical response in any two species. There are at least two classes of these principles: (1) the true anterior pituitary gonadotropic principle which may have its derivation directly from the anterior lobe of the pituitary or indirectly from the serum of the pregnant mare; (2) and another group derived either from pregnancy urine or from the placenta, such principles being designated anterior pituitary-like gonadotropic. The pharmacologic action of these two classes is not the same. There is evidence that the anterior pituitary-like principle is active only in an animal with an intact pituitary, while the one from the anterior lobe produces ovarian changes in the hypophysectomized animal, apparently substituting for the absent pituitary. Basic chemistry of the gonadotropic principles has not progressed in a manner comparable to that of the ovarian and testicular hormones. These gonadotropic principles are not available in pure form, but contain various contaminants. It is believed generally that these substances are of complex protein nature. Some few investigators count as many as six gonadotropic principles from the anterior pituitary, but the majority of workers believe that, perhaps, the total number of hormones actually elaborated by the anterior lobe is less than this figure.

*Presented by invitation, at the Sixty-Second Annual Meeting of The American Gynecological Society, Swampscott, Mass., May 21 to June 2, 1937.

fore the factors concerned with bleeding in normal menstruation have been definitely determined. I should like to draw your attention again, however, to the increase in the estrogenic hormone content of the blood which is associated with the onset of bleeding in patients with hyperplasia. This represents a departure from the normal and may prove of considerable significance.

DR. WILLIAM P. HEALY, NEW YORK, N. Y.—We have over a period of fifteen years seen many uteri at or beyond the menopause which were of the subinvolution type, free from myomas, and from which we have obtained a gross amount of endometrial tissue which suggested the probability of cancer and in which in each instance we have placed radium within the uterine cavity in a dosage running from 1,000 to 1,400 millicurie hours. The pathologist has examined the tissue in all of the cases and often failed to find cancer. Instead he has reported hyperplastic glandular endometrium to our surprise. In no single instance has cancer to our knowledge subsequently developed, despite the large amount of endometrial tissue present and its intense hyperplastic structure. The rather small amount of initial uterine radiation, not exceeding 1,400 millicurie hours, has apparently permanently prevented the development of cancer in these cases.

DR. NATHAN P. SEARS, SYRACUSE, N. Y.—We have seen specimens of curettings in the laboratory where many sections show the "Swiss-cheese" type of gland, but in which if we block every bit of tissue we find a small area of carcinoma. Diagnosis from a frozen section of curettings is, I think, an extremely hazardous procedure.

Two years ago I was called to examine a frozen section of curettings removed from a patient upon whom an interposition operation was about to be done. I studied several slides and found nothing but benign hyperplasia. I reported this, stating the danger of such an examination, and asked that the operation be postponed until the next day when I could study more satisfactory slides of all the material. In spite of this, the interposition operation was done and the final section showed definite adenocarcinoma of the corpus. This clearly emphasizes the importance of studying all the material removed by the curette.

DR. FRANKLIN L. PAYNE (closing).—Dr. Fluhmann's statement that it is unnecessary to enlist the function of the anterior lobe to explain the development of hyperplasia is probably correct. The commonly accepted explanation of hyperestrinism, however, does not account for the presence of postmenopausal hyperplasia in the absence of demonstrable pelvic pathology. The alternatives which I suggested were mentioned as possibilities and not as truisms.

Search for evidence of blood dyscrasia is our routine procedure in all instances of functional bleeding in young women. Careful estimation of the thyroid function, both clinically and by basal rate determinations, is also done, for we have learned that thyroid deficiency plays an important rôle in the etiology of functional hemorrhage. In our experience one-half of the adolescent hemorrhages are accompanied by hypothyroidism, and the same condition exists in approximately one-fifth of those in the third decade of life.

Dr. Novak's emphasis upon the possible association of postmenopausal hyperplasia and malignancy is important. The absence of a return of bleeding in our patients with postmenopausal hyperplasia, during periods ranging from one to twelve years after the curettage indicates, in this group at least, that the hyperplasia did not predispose to the development of carcinoma.

As to the photomicrograph which was questioned by Dr. Martzloff, it is difficult to show all the characteristics of hyperplasia in one lantern slide. I am certain, however, that should Dr. Martzloff study all of the tissue from which the questionable slide was made he would concur in my diagnosis.

hydatidiform mole or chorionepithelioma is suspected, since these two abnormalities of pregnancy show consistent high concentrations of gonadotropic principles. One must feel certain of the length of pregnancy before a correct inference can be drawn. George Van S. Smith⁵ has reported an increase of these principles in pre-eclampsia and eclampsia. One expects an increased production of true pituitary gonadotropic principles in hyperpituitarism. We know that these are excreted in the urine following the menopause, but here, of course, the depressing effect of the ovary on the pituitary has been removed in part.

On reviewing all these factors, we find reported little evidence of change in the ovaries. The ovaries of women dying of eclampsia or during pregnancy show no increased degree of luteinization over that in the normal pregnant states. Multiple

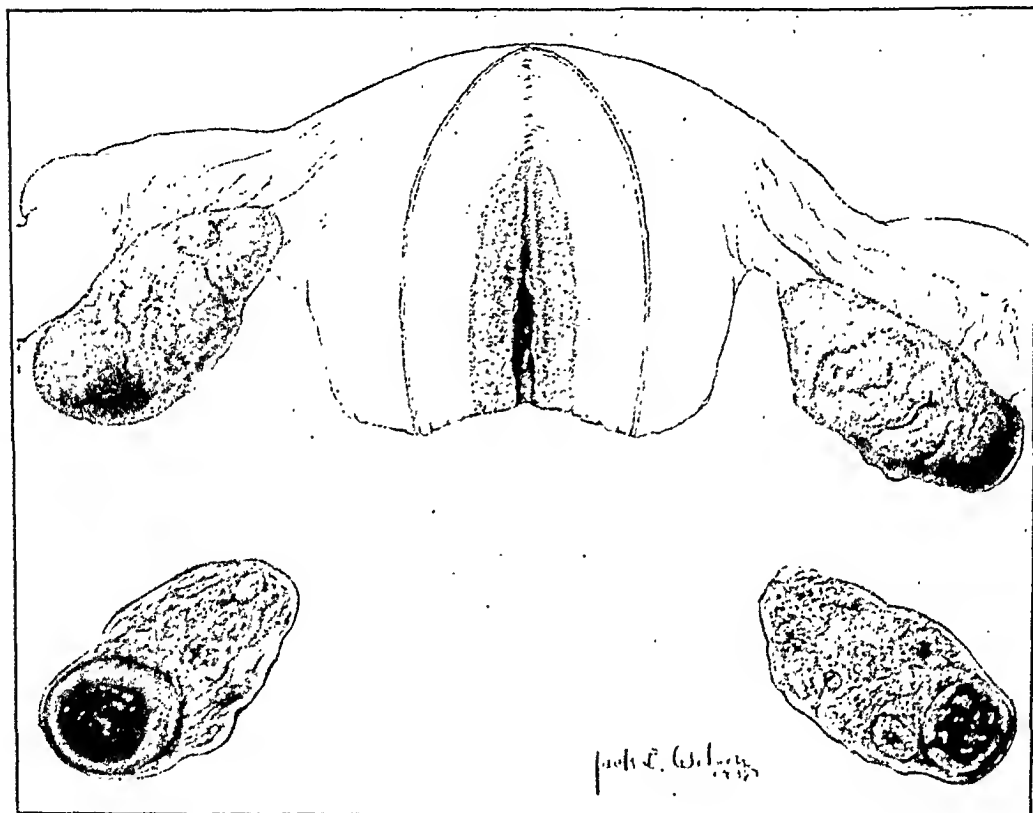


Fig. 1.—Case 1. Patient with regular menses who received 5,250 R. U. gonadotropic principle of pregnancy urine and was operated upon during the third week of the cycle. Ovaries showed three corpora lutea. A biopsy of the endometrium before treatment was begun showed an early progestational effect. This is the artist's drawing of the specimen after operation. Where the ovaries were studied only at operation, a similar drawing was made and became a part of the record. ($\times 40$.)

cysts are reported in hydatidiform mole and chorionepithelioma, but this finding is not constant. Most of the patients with pituitary tumors are seen in the later hypopituitary stage where there is little chance for hyperluteinization. Wagner⁶ reports the presence of multiple lutein cysts of the ovaries and of progestational endometrium associated with amenorrhea in a woman who had a tumor of the pars glandularis of the pituitary.

Another method of study which has the advantage of being fairly well controlled is that of studying the ovarian responses after injections of gonadotropic principles. The effect may be evaluated by direct observation and study at laparotomy of ovaries following such treatment (Fig. 1); by indirect interpretation of ovarian

The employment of trade names which often do not indicate the source of these preparations and the use of varying units for the expression of potency have led to much confusion in the minds of clinicians. There are three methods which are used generally by American pharmaceutical concerns to estimate gonadotropic function and in which the female immature mouse or rat is employed. The ovaries may be observed directly for evidence of follicle stimulation or information may be gained indirectly by vaginal smears to determine the onset of estrus. The ovaries may be observed directly for evidence of luteinization, or the ovaries may be weighed and weight changes regarded as evidence of gonadotropic effect. There is no definite relationship between weight increase, the induction of vaginal estrus, and the luteinizing effect. As a further source of confusion, some products are available in rat units and some in mouse units. There is some disagreement in the relationship between these units. Van Dyke quotes a ratio between a mouse and rat unit as 1 to 4, while Zondek believes it to be 1 to 6 or 8. Since these principles are used clinically most often in an attempt to produce luteinization and since the corpus luteum unit is employed most frequently, this unit has been adopted by us as a common denominator for gonadotropic activity. It is our practice to re-assay the extracts which we use in terms of this corpus luteum formation unit. Such a practice has resulted in some interesting observations. In a preparation that contained 8,000 vaginal estrus rat units per c.c., we found only 200 corpus luteum rat units. In a preparation that was said to contain 2,000 luteinizing units per c.c. determined by microscopic study of the ovaries, we found only 200 corpus luteum rat units by the method of gross inspection.

METHODS OF STUDY

With differences in response so apparent in the various laboratory animals, a study of human ovaries following the administration of gonadotropic principles obtained from placenta and pregnancy urine seemed justified. The rather general use clinically of certain such commercial preparations and the equivocal results reported by many seemed to urge a careful consideration of the possible method of action, if any, of such preparations. With the various hemorrhagic and lutein changes seen in the ovaries of rodents in mind, we were led at the early part of this study to question the possibility of serious damage to the human ovary from such administrations.

In the human being some opportunities are present which may permit an insight into the ovarian effects of these gonadotropic principles.¹ We would expect to find these principles in the blood and urine of the newborn. Engle² has shown this to be true. Gonadotropic principles are present in pregnancy. The works of Evans³ and of Browne,⁴ especially the quantitative aspects, have been most enlightening. Evans found a consistent early "peak phenomenon" in normal pregnancy. The highest daily urinary output at this peak in one instance was 1,040,000 R. U. and the lowest was 75,000 R. U. This peak is reached rapidly and is usually highest at about the thirtieth day after their appearance. By the sixty-fifth day, the concentration is usually below 10,000 R. U. and approximates this figure for the remainder of pregnancy. These observations necessitate a careful interpretation in instances where

the interpretation of the endometrial pictures. Some of the endometrial patterns diagnosed as hyperplasia of the endometrium did not show this alteration. In three patients the report of corpora lutea proved to be either persistent lutein tissue or lutein cyst. One patient approaching the menopause who had hyperplasia of the endometria did show a corpus luteum. However, she had treatment over a period of several weeks, repeated vaginal examinations and two curettements. These physical factors might have encouraged ovulation.

The very definite problem of improving the patient is constant. In an effort to relieve the woman who had bleeding as a symptom and to aid in the evaluation of other methods of treatment, a program of varied therapeutic measures was instituted. The various "levels" at which therapy could be directed, the various agents that were used and the results, were reported.¹³ This furnished a valuable series for comparison.

These studies re-emphasized the fact that there is a variance in the criteria for the diagnosis of hyperplasia of the endometrium. When one is endeavoring to correct the condition of irregular bleeding, one should know if the patient is bleeding because of some irregularity of the ovarian cycle. One should be familiar with the therapeutic agent that is employed and should be able to interpret the response to therapy. To help us with these factors, a study of 358 consecutive patients with functional irregularities of the menses was made. Clinical data, endometrial histology, and follow-up records were correlated. A clinical classification of functional irregularities of the menstrual cycle which emphasized etiology and which was in harmony with the present concepts of the histology, physiology, and hormonology was attempted.

As a therapeutic agent there could be two sources of benefit from the use of these principles; the stimulating effect itself and the production of estrin and progesterin. To obtain a substitutional effect, one could suppose that there was some alteration of the pituitary gland or that the production of these principles during pregnancy has been stopped. Most observers will agree on the value of substitutional endocrine therapy, but the matter of gland stimulation is subject to debate. If the gonadotropic principles meet the suggestions given above, they will do more than most endocrine principles. Several clinical conditions suggest themselves as likely to be benefitted, one of which is hypogonadal syndromes which are known to be due to inadequate gonad function; if in these instances the ovary is the influencing factor, and, if it could be stimulated to normal endocrine and exocrine function, such an individual would develop into a normal sexually mature state. The same is true in certain instances of sterility. Other clinical indications would be indirect, in that they would be dependent upon the elaboration of estrin and progesterin in quantities approaching normal and would be found in varying degrees when the ovary had failed in this function. Such conditions would probably have as a symptom menorrhagia, metror-

function from endometrial studies (Fig. 2); and by the clinical responses to such therapy of certain patients with hypogonadal syndromes and hypofunctioning ovarian states.

J. S. L. Browne has been able to estimate the progestin excretion by determining the pregnandiol content of the urine. This product represents a conjugated inactive form of progestin which does not respond to the biologic tests, but which may be precipitated and actually weighed. An employment of such pregnandiol estimations after gonadotropic therapy would probably be another method of arriving at information regarding the luteinizing effects of these principles.

In the past blood and urine hormone assays in the so-called hypo-functioning states, before and after therapy, have yielded little information of value regarding the clinical effectiveness of these principles.

The electric potentiometer method as employed by Allen and coworkers⁷ for evidence of ovulation is certainly conclusive in animals but, as yet, its clinical employment has not been described. The work of Knauss⁸ on manometric studies of the

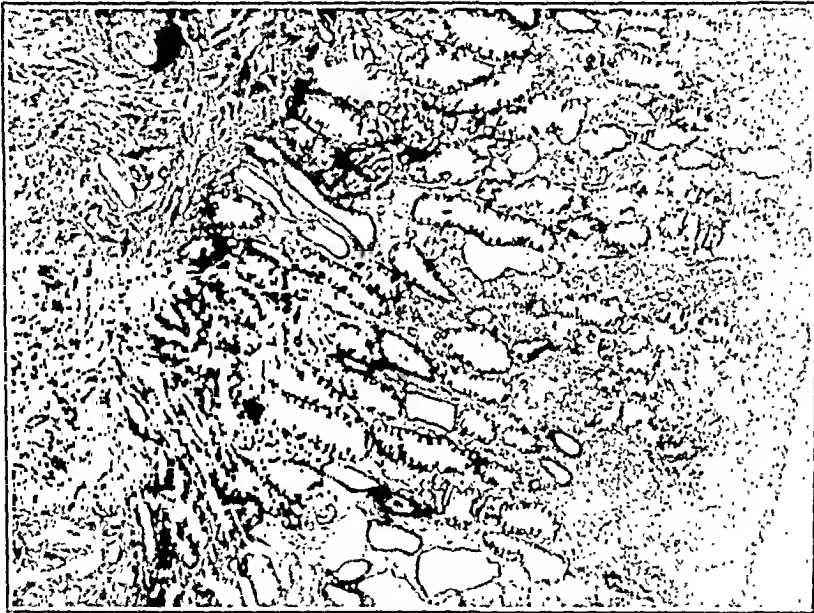


Fig. 2.—This is the endometrial picture of Case 1 after therapy. Here the menstrual history of ovarian response and endometrial pattern are in agreement. The endometrium here was taken from the uterus after operation. If the uterus had not been removed, the endometrium would have been studied by curettage. ($\times 40$.)

uterus might permit another index as to the occurrence of ovulation and corpus luteum formation. The recent work of Kurzrok and coworkers,⁹ however, has thrown doubt on the so-called quiet stage in uterine contractility in the nonpregnant uterus. In their hands progesterone was observed at times to produce uterine contractions. In both of these experiments there is a valid objection to having a foreign body in the uterus.

DISCUSSION

We have been seven years accumulating data for this study. A report dealing with therapy¹⁰ suggested the need of more exact information regarding the ovarian and endometrial response to therapy. During the progress of this work several related problems presented themselves for solution. The summation of this data required a complete review of our related material. We found that some of our deductions in previous papers^{11, 12} were incorrect due to a difference in

"anovulatory bleeding" as diagnosed by us (Fig. 3). We have examined the material scrupulously because the results are dependent upon our ability to make the diagnosis of anovulatory bleeding correctly. The therapeutic reasoning here is apparent: simply that of preventing a halt anywhere in the normal progress of maturation of the follicle and the subsequent phenomena. The chance of error lies in the frequency and facility with which the diagnosis of a primary alteration of the ovarian function is made. This has been emphasized and our method of frequent endometrial biopsies helps overcome this difficulty. We have purposely refrained from trying "augmentor" or "synergistic" effect.



Fig. 5.

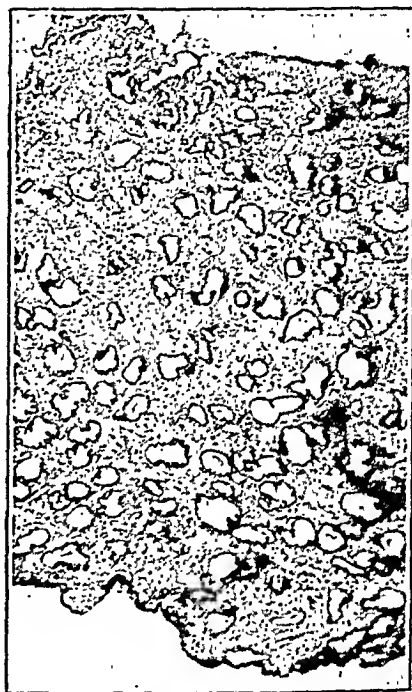


Fig. 6.

Fig. 5.—This is a higher magnification of the ovary in Case 2 which simply verifies the presence of a normal corpus luteum. (X40.)

Fig. 6.—The endometrial pattern in Case 3 which completes the study. Here we have evidence of progestational response. (X40.)

There has been no mixing of these principles with other hormones, elements, or compounds. We have simply tried to compare the effect on the human ovary and endometrium with that of the experimental animals which showed the alterations that predicated the present therapeutic concepts. We consistently used doses greater than those prescribed.

PRESENTATION OF DATA

The data which follow are obtained from observations made upon 85 patients who had received treatment with these principles. A large part of these data has been reported upon at various times. The present report is based upon a complete review and reevaluation of all the

rhagia, or amenorrhea. In these conditions we should find an ideal "proving ground" for substances supposed to stimulate and luteinize the ovary. The condition of anovulatory bleeding meets the requirements for a therapeutic reaction. There is a failure in the ovarian cycle which gives both direct and indirect evidence. An agent is used and

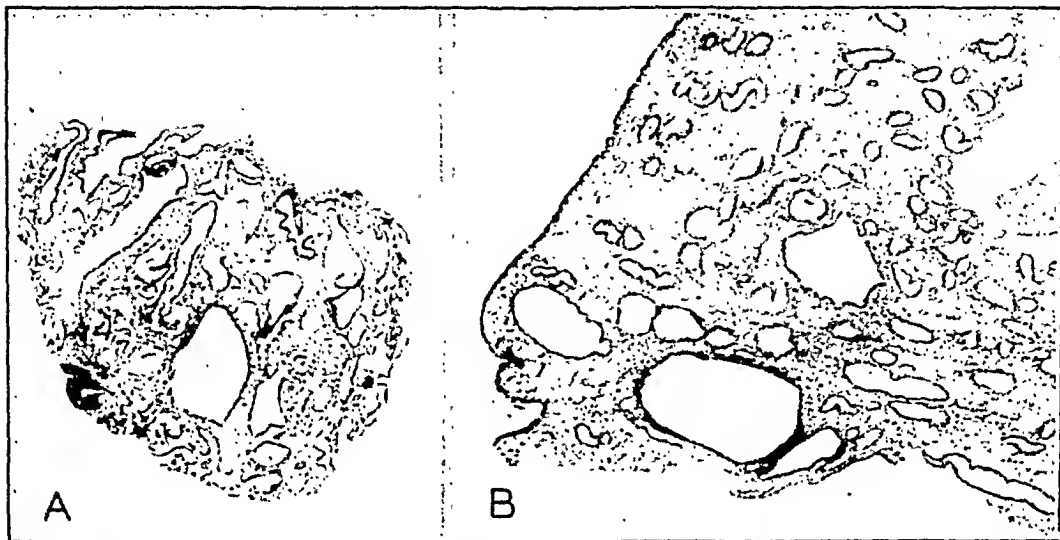


Fig. 3.—Case 2. *A*, May 4, 1937, biopsy before treatment (bleeding). *B*, May 12, 1937, curettement after treatment with 6,000 R. U. of a gonadotropic principle of pregnancy urine given on day of biopsy (not bleeding). Febrile reaction (38°) during treatment. Hyperplasia of the endometrium. No changes after therapy. These figures are representative of the tissue patterns that are obtained by biopsy technique. ($\times 40$.)



Fig. 4.—Case 3. Patient with oligomenorrhea who received 21,000 R. U. of a gonadotropic principle of pregnancy urine during the thirtieth to thirty-fourth day of her cycle. Both ovaries were available for study. These were photographed in the gross, sectioned, stained, and studied under a magnification of $\times 10$. This figure shows two corpora lutea in the ovary. ($\times 10$.)

the characteristic effect should be forthcoming. In this instance it would be rupture of the follicle and corpus luteum formation in the ovary and characteristic endometrial changes of the progestational type. We have purposely chosen the majority of our patients from the

TABLE II

DURATION OF TREATMENT DAYS	SOURCE OF GONADOTROPIC PRINCIPLES	TOTAL DOSE	CLINICAL EFFECT	ENDOMETRIUM AFTER TREATMENT	OVARIES
<i>Amenorrhea</i>					
4	Gland	220 R. U.	None	Not studied	No corpus luteum
4	Gland	480 R. U.	None	Phase of prolonged acyclic estrin action	Not studied
8	P. U.	2,400 R. U.	None	Curetage (no tissue available)	No corpus luteum
3	P. U.	3,000 R. U.	None	Not studied	No corpus luteum
3	Placenta	1,750 R. U.	None	Estrin arrest	No corpus luteum
<i>Oligomenorrhea</i>					
4	P. U.	21,000 R. U.	(41st day of cycle)	Progestational phase (irregular ripening)	Three corpora lutea
10	Placenta	6,750 R. U.	(50th day of cycle)	Estrin arrest	Lutein cysts
<i>Postmenopausal</i>					
6	Gland	300 R. U.	None	Not studied	Sclerotic ovaries
10	P. U.	5,800 R. U.	None	Estrin arrest	No corpus luteum No corpus luteum
<i>Premenarcheal</i>					
3	Gland	140 R. U.	None	Not studied	No corpus luteum
4	P. U.	1,600 R. U.	None	Not studied	No corpus luteum
6	P. U.	3,200 R. U.	None	Estrin arrest	No corpus luteum

material available. More recent observations after higher dosage are included. The procedures carried out in our routine study of patients and tissues have been stated in another paper. Our method of studying the material by gross and microscopic observation and ova interpretation of changes before and after treatment is shown by the illustrations and our method of reasoning is given in the tables (Figs. 4, 5, and 6).

From the tables one can see that there has been sufficient material surveyed to warrant a fairly comprehensive study. Most of the available preparations were used. The age of the patients varied from eleven to sixty years, and the parity

TABLE I. REGULAR MENSES

DURATION OF TREATMENT DAYS	SOURCE OF GONADOTROPIC PRINCIPLES	TOTAL DOSE	ENDOMETRIUM AFTER TREATMENT	OVARIES
<i>First Week</i>				
3	Gland	180 R. U.	Progestational phase	Corpus luteum
3	P. U.	1000 R. U.	Estrin phase	Corpus luteum
3	P. U.	1600 R. U.	Estrin phase	No observation
3	Serum	2000 M. U.	Estrin phase	No corpus luteum
<i>Second Week</i>				
2	Gland	100 R. U.	Not studied	Corpus luteum
3	Gland	140 R. U.	Not studied	No corpus luteum
3	Gland	140 R. U.	Not studied	Corpus luteum
2	P. U.	800 R. U.	Progestational phase	Corpus luteum
4	P. U.	1200 R. U.	Late estrin phase	No corpus luteum
5	P. U.	1600 R. U.	Progestational phase	Corpus luteum
12	P. U.	2600 R. U.	Progestational phase	Corpus luteum
8	P. U.	2700 R. U.	Progestational phase	Corpus luteum
<i>Third Week</i>				
7	Gland	360 R. U.	Not studied	Corpus luteum
8	P. U.	2400 R. U.	Progestational phase (irregular ripening)	No corpus luteum (observation grossly of ovaries)
5	P. U.	3000 R. U.	Progestational phase	Corpus luteum
9	P. U.	4000 R. U.	Progestational phase	Corpus luteum
5	P. U.	4400 R. U.	Progestational phase (marked edema)	Corpus luteum
4	Placenta	2750 R. U.	Progestational phase (irregular ripening)	Corpus luteum
4	Placenta	3000 R. U.	Progestational phase (irregular ripening)	Corpus luteum
8	Placenta	5250 R. U.	Progestational phase (irregular ripening)	Three corpora lutea
3	Serum	2000 M. U.	Progestational phase	Corpus luteum
<i>Fourth Week</i>				
4	Gland	300 R. U.	Not studied	Corpus luteum
8	P. U.	2100 R. U.	Not studied	No corpus luteum (ovaries studied by inspection only)
5	P. U.	3000 R. U.	Progestational phase (irregular Menstrual phase	Corpus luteum
5	P. U.	4400 R. U.	ripening)	Corpus luteum

TABLE III

URATION OF TREATMENT DAYS	SOURCE OF GONADOTROPIC PRINCIPLES	TOTAL DOSE	CLINICAL EFFECT	ENDOMETRIUM AFTER TREATMENT	OVARIES
<i>Menorrhagia</i>					
3	Gland	160 R. U.	Operation	Progestational phase	Corpus luteum
3	Gland	180 R. U.	Operation*	Estrin arrest	No corpus luteum
3	Gland	180 R. U.	Operation	Estrin arrest	No corpus luteum
4	Gland	180 R. U.	None	Estrin arrest (infection)†	Corpus luteum
4	Gland	360 R. U.	None	Estrin arrest	Not studied
5	Gland	360 R. U.	None	Estrin arrest†	Corpus luteum
4	Gland	540 R. U.	Stopped	Estrin arrest	Not studied
8	P. U.	2,400 R. U.	None	Prolonged acyclic estrin phase	No corpus luteum
5	P. U.	2,800 R. U.	Operation	Estrin arrest	No corpus luteum
4	P. U.	3,000 R. U.	None	Estrin arrest, before and after treatment (infection)	No corpus luteum
8	P. U.	3,000 R. U.	None	Prolonged acyclic estrin phase	Corpus luteum
4	P. U.	3,200 R. U.	None	Prolonged acyclic estrin phase	Corpus luteum cyst
7	P. U.	6,600 R. U.	None	Prolonged acyclic estrin phase	No corpus luteum
7	P. U.	7,400 R. U.	None	Prolonged acyclic estrin phase	No corpus luteum
9	P. U.	8,200 R. U.	None	Estrin arrest	No corpus luteum
10	P. U.	9,500 R. U.	None	Estrin arrest	No corpus luteum
5	Placenta	2,500 R. U.	Stopped	Estrin phase (menstrual phase before R.)	No corpus luteum
<i>Metrorrhagia</i>					
1	Gland	60 R. U.	Operation	Estrin arrest	No corpus luteum
4	Gland	170 R. U.	Stopped	Estrin arrest	Not studied
6	Gland	180 R. U.	Operation	Estrin arrest	No corpus luteum
4	Gland	240 R. U.	None	Estrin arrest	Not studied
3	Gland	270 R. U.	None	Menstrual phase (before and after R.)	Not studied
4	Gland	270 R. U.	None	Prolonged acyclic estrin phase (estrin arrest before R.)	Not studied

*Operation (D. and C.) necessary to stop bleeding or done for diagnosis and not permitting interpretation.

†Cyclic polymenorrhea no biopsy before R.

was from 0 to 15. The menstrual histories extended from childhood through the regular and irregular menstrual phenomena to senility. The total material available for analysis at present includes observations upon 85 patients, distributed according to menstrual histories as follows: Regular, 22; amenorrhea and oligomenorrhea, 7; menorrhagia, metrorrhagia and polymenorrhea, 51; postmenopause, 2; and premenarche, 3. The ovaries of 57 patients were studied either grossly or grossly and

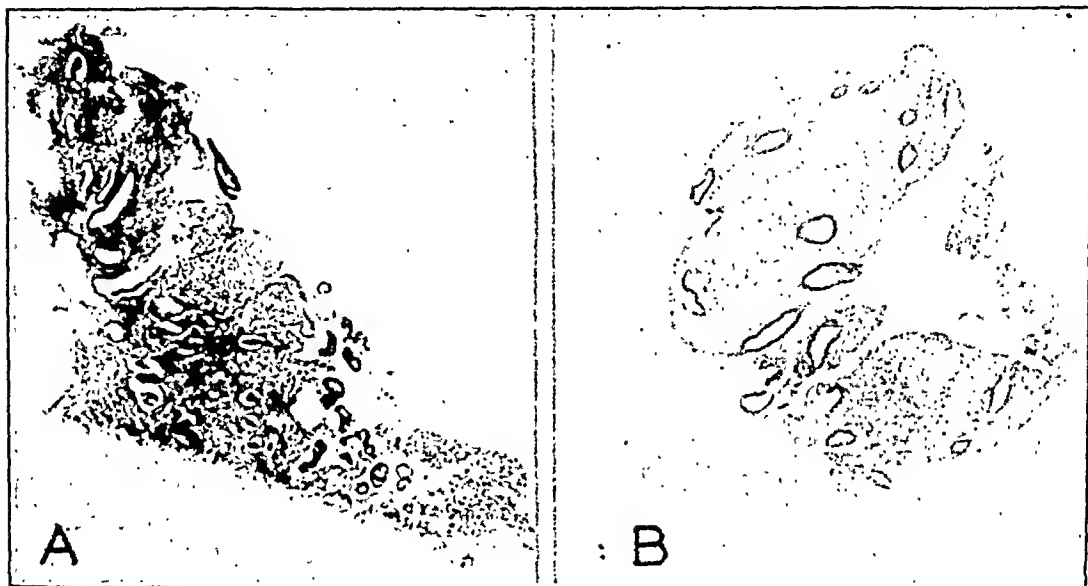


Fig. 7.—Case 5. *A*, May 17, 1937, biopsy before treatment (bleeding). *B*, May 25, 1937, curettement after 14,000 R. U. of a gonadotrophic principle of pregnancy urine over a period of two days (not bleeding). Severe febrile reaction (40.4°) during treatment. No change in the endometrial pattern. ($\times 40$.)

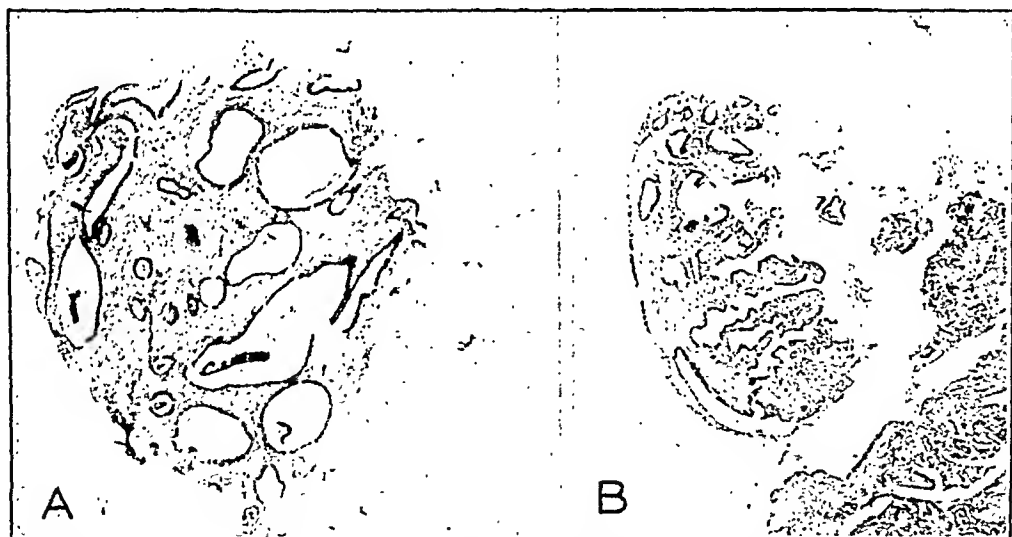


Fig. 8.—Case 4. This patient had menometrorrhagia as a symptom, and the bleeding was diagnosed as anovulatory type. She received 1,800 R. U. of gonadotropic principle of pregnancy urine. *A*, represents the endometrial biopsy before treatment (bleeding). *B*, is the curettement after treatment (still bleeding) six days later. There is some question as to the endometrial picture in *B*. We thought it was suggestive of a progestational response though the bleeding increased under therapy and a curettement was necessary. ($\times 40$.)

microscopically, while in 74 patients the endometrium was studied either alone or in conjunction with the ovaries. Gonadotropic principles from the anterior lobe or from the serum of pregnant mares were employed in 34 patients; similar principles from pregnancy urine or placenta were used in 51 patients. The total doses of the former

TABLE IV
Preparations

1. ANTERIOR PITUITARY GONADOTROPIC
2. DANISH GONADOTROPIC SERUM
3. PLACENTAL GONADOTROPIC PRINCIPLE
4. DANISH ANTERIOR PITUITARY-LIKE PRINCIPLE
5. ANTERIOR PITUITARY-LIKE PRINCIPLE FROM PREGNANCY URINE

<i>Age</i>		<i>Parity</i>	
11-15	4	0	24
15-20	15	1-3	20
21-40	48	4-15	41
41-44	15		
45-60	3		
Total	85		

<i>Menses</i>		<i>Dosage</i>	
Regular	22	Smallest total dose	60 rat units
Amenorrhea and oligomenorrhea	7	Largest total dose	24,250 rat units
Menorrhagia, metrorrhagia and polymenorrhea	51		
Postmenopause	2		
Premenarche	3		
Total	85		

Duration of Treatment

Shortest time of treatment	1 day
Longest time of treatment (at one period)	87 days

Method Employed for Study

Biopsy technique and curettement	74
Gross and microscopic study of ovaries	57
Endometrium following hysterectomy	32
Inspection of ovaries	4

ranged from 100 R. U. to 4,400 M. U., the daily dose varying from 20 R. U. to 800 R. U. Of the pituitary-like principles the total doses varied from 250 R. U. to 24,250 R. U., the daily dose from 100 R. U. to 8,000 R. U. The period of treatment lasted from one to eighty-seven days. The longest period of observation was two and one-half years. Four methods of administration were tried in an effort to duplicate the various phenomena: (1) small daily doses over a short period, (2) small daily doses over a long period, (3) large daily doses over a short period, and (4) large daily doses over a longer period.

Six patients with amenorrhea showed no response in the endometrium and no corpus luteum in the ovaries. The largest dose was 3,000 R. U. and the longest interval of treatment eight days. One patient with oligomenorrhea showed irregular progestational ripening and three corpora lutea after four days of treatment, beginning on the forty-first day of the cycle and totaling 21,000 R. U. Another showed no change after ten days' treatment beginning on the fiftieth day of the cycle. This is not conclusive as the first patient had a varying cycle, and we cannot claim that

TABLE III—CONT.

DURATION OF TREATMENT DAYS	SOURCE OF GONADOTROPIC PRINCIPLES	TOTAL DOSE	CLINICAL EFFECT	ENDOMETRIUM AFTER TREATMENT	OVARIES
<i>Metrorrhagia—Cont.</i>					
6	Gland	340 R. U.	Stopped	Prolonged acyclic estrin phase	Not studied
3	Gland	350 R. U.	None	Menstrual phase† (irregular tissue shedding)	Not studied
6	Gland	360 R. U.	None	Prolonged acyclic estrin phase	Not studied
9	Gland	460 R. U.	None	Estrin arrest	Not studied
87	Gland	500 R. U.	None	Estrin arrest	Not studied
4	Gland	600 R. U.	Decreased	Estrin arrest	Not studied
3	Gland	800 R. U.	Stopped	Estrin arrest	Not studied
3	Gland	840 R. U.	Stopped	Prolonged acyclic estrin phase	Not studied
7	P. U.	600 R. U.	Operation	Estrin arrest	Not studied
2	P. U.	1,000 R. U.	Not bleeding	Prolonged acyclic estrin phase	Not studied
7	P. U.	1,400 R. U.	None	Prolonged acyclic estrin phase	Not studied
50	P. U.	1,800 R. U.	None	Prolonged acyclic estrin phase	Not studied
6	P. U.	3,600 R. U.	None	Estrin arrest	Not studied
4	P. U.	4,700 R. U.	None	Endometritis	No corpus luteum
6	P. U.	5,400 R. U.	None	Progesterational phase (irregular ripening, before and after R)	Corpus luteum
1	P. U.	6,000 R. U.	Stopped	Estrin arrest	Not studied
7	P. U.	7,000 R. U.	Increased	Prolonged acyclic estrin phase	Not studied
10	P. U.	7,000 R. U.	Slight decrease	Estrin arrest	Not studied
2	P. U.	14,000 R. U.	Slight decrease	Estrin arrest	Not studied
5	P. U.	18,000 R. U.	Little	Prolonged acyclic estrin phase	Not studied
8	P. U.	24,250 R. U.	Decreased	Estrin arrest	Not studied
2	Placenta	250 R. U.	Stopped	Estrin arrest	No corpus luteum
3	Placenta	2,000 R. U.	Stopped	Hypocestrin phase	No corpus luteum
3	Placenta	2,250 R. U.	Operation	Estrin arrest	Lutein cyst
6	Serum	4,400 M. U.	None	Prolonged acyclic estrin phase	Not studied

†Progesterational phase with irregular ripening before treatment.

24,000 R. U., the findings were quite suggestive. This leads us to think that the desired reaction, if it occurs at all, will most likely follow large doses rapidly repeated over a fairly short period of time. We also think that the concentration and dosage must approach the requirements recognized in estrin therapy.

Certainly in this group of females between the ages of eleven and sixty, who had gynecologic complaints that required hospitalization, we should find ample opportunity for benefit and syndromes that would give visible response. Clinical improvement in a few instances was seen and recorded, but histologic response on the part of the ovaries and endometrium was most problematic.

In many women who have irregular bleeding as a symptom it has been our experience that there are often found complicating factors and that the correction of these altering conditions increases the chances for lasting relief. Altered position, altered blood and nerve supply, and abnormal anatomy and histologic changes are usually interpreted in terms of abnormal function. We feel that in the great majority of instances the pituitary is normal. In most instances the ovary receives adequate pituitary stimulation. The opportunity for failure in the ovary is greater. The more influencing factors and functions the greater chance there is for derangement. An abnormal ovary would hardly respond in a normal manner to an injected principle, and when we have a normal ovary the injected hormone is not needed. Our first fear in this problem was that we might find some harmful effect on the ovary from the use of these principles. Our present concern is finding any histologic effect from their use. Certainly in the doses that we have employed, we feel on much safer prognostic ground, when we find low-grade pelvic cellulitis, oophoritis, nutritional changes, displacements of the ovary, an abnormal uterus, low-grade infection of the ovary, and interference of ovarian blood supply or any other local cause that may influence the ovary.

SUMMARY

A discussion of these gonadotropic principles with an explanation for the confusion associated with their potency is given.

The presence of these principles in the human blood and urine under normal and abnormal circumstances is discussed.

The applicable evidence of ovulation and corpus luteum formation is reviewed.

The rationale of gonadotropic hormone therapy is given.

The data on 85 patients who were studied following injections of gonadotropic principles are presented. We have found and corrected a source of error in one of our previous reports.

Our conclusions are submitted.

the response was due to the injection (Case 3). Two postmenopausal patients showed no ovarian nor endometrial response and no menstruation. The maximum dose was 5,800 R. U. in ten days' treatment. In the three preadolescent patients who had never menstruated, there were no corpora lutea. The largest dose was 3,200 R. U. given in six days. None of them menstruated. The 22 patients with regular menses were grouped according to the week of the cycle in which the operation was performed. The largest dose was 5,250 R. U. and the longest period of treatment was twelve days. In most instances we were able to predict correctly the endometrial pattern and the histology of the ovary (Case 1). In another study we attempted to gain information as to the time of ovulation in untreated patients. Thus, we had a large number of controls and there was no appreciable variation in the ability to predict the pictures, when the week of the cycle was known in the two groups. Therefore, we can say from our observation, there was no varying of the cycle in the patient with regular menses. The ovaries of two patients showed more than one corpus luteum, but we hesitate to designate the ages of them. Fifty-one patients had menorrhagia, metrorrhagia, and polymenorrhea. The longest period of treatment at this time was ten days and the largest dose was 24,250 R. U. Bleeding stopped in six instances within three to six days, but the endometrium showed either late estrin arrest or a phase of prolonged acyclic estrin action. Eight patients were operated upon after three to five days' treatment. The ovaries were studied in 21 of the 51 patients. In 15 there were no corpora lutea present. In two there were old luteal cysts. In one a corpus estimated as "recent" with irregular progesterational ripening of the endometrium was found. In three there were recent corpora lutea. Two of these had only 160 and 180 R. U. each and were operated upon on the third day. One had late estrin arrest of the endometrium, and the other had late progesterational phase before therapy. In analyzing these 51 patients, we are unable to reconcile clinical response with the histologic picture. In only one (Fig. 7) or possibly two instances, did we find the endometrial pattern altered under therapy. In none of the instances where bleeding was checked did we find evidence of progesterational response in the endometrium (Fig. 8). Novak has explained this apparent paradox.

In the three girls from eleven to fifteen years, we most certainly did not want to find a reaction similar to the Aschheim-Zondek test, but we found no effect that we could interpret. One would think that these cases would be ideally suited for observations dealing with maturing and stimulating factors.

Our experience in the general treatment of amenorrhea parallels that of others. By one or several combinations of a great many agents, we are able to get a patient to bleed once or twice, then the treatment becomes futile. In this group we have purposely picked only those patients who had no previous endocrinal therapy. In the above two groups and in the postmenopausal patients, we found no change in the ovaries or endometria due to the doses of gonadotropic principles given. Clinical improvement from the use of these preparations is probably most often reported in the group of patients who have menometrorrhagia as a symptom. In this group 8 of the 51 (16 per cent) patients stopped bleeding. This figure can be equalled or bettered by any of the other treatments for uterine bleeding. The rational effect here would be the production of lutein tissue with an associated progesterational reaction and shedding of the mucous membrane. In small doses we have not been able to show this. In one patient who was given

DISCUSSION

DR. M. EDWARD DAVIS, CHICAGO, ILL. (by invitation).—From a great deal of experimental data upon the gonadotropic hormones a few definite conclusions can be drawn. In the first place, the anterior pituitary gland produces a hormone or hormones which are vastly different in their gonadotropic action from the anterior pituitary-like gonadotropic hormone present in such an abundance in the urine of pregnancy. In the second place, the urine of women following castration or the menopause contains a gonadotropic hormone which is almost a pure follicle stimulator and thus resembles very much the follicle-stimulating fraction of the anterior pituitary gland hormone. In the third place, in order that ovulation be produced experimentally in hypophysectomized animals, it is necessary first to produce growth of follicles by a follicle-stimulating hormone and then to administer the luteinizing fraction. If the latter is not given, mature follicles do not ovulate but undergo retrogression. Successful experiments in the production of experimental ovulation in monkeys have been reported by Hisaw and his group and Christian Hamburger.

Up to the present, no successful artificial ovulation has been reported in the human female. This physiologic process which can be duplicated experimentally with relative ease in laboratory animals has been difficult to carry out in the human species. It is obvious that the production of ovulation is necessary for the completion of the normal cycle. Undoubtedly many pathologic conditions seen in women are the result of, or are influenced by, the absence of ovulation.

About a year ago we became interested in a gonadotropic hormone derived from the blood serum of pregnant mares. Cole and Hart observed that during a limited period of pregnancy in mares there is present in high concentration a gonad-stimulating substance. The concentration reaches its maximum at about the sixty-fifth to the seventieth day of the gestation. Biologic studies on this substance have established distinct differences between it and other gonad-stimulating substances. It is not excreted in the urine of the mare at any time during pregnancy. It is not ultrafiltrable through collodion membranes, as is pregnancy urine substance, and it is therefore probably of a higher molecular weight. In general, it closely resembles in its gonadotropic activity the extracts of the anterior hypophysis. Thus, it was found that ovulation could be produced in young ewes during the estrus season and that a second dose of serum given seventeen days later resulted in a second ovulation with estrus which was followed by pregnancy when the ewes were mated. Similarly, mare serum injected in young sows produced ovulation and estrus, and, when the animals were bred, pregnancy followed. From these and many other experiments one can conclude that the gonadotropic hormone obtained from pregnant mare serum will cause follicular growth and luteinization with little or no degenerative changes in the ovary, so that it closely resembles the hormone derived from the anterior pituitary gland.

Carlund of the Upjohn Laboratories has successfully purified the gonadotropic mare serum substance so that the protein fraction has been almost eliminated. Furthermore, they have standardized the dose so that the rat unit represents the amount of hormone which, when divided into three daily subcutaneous doses and injected into twenty-one- to twenty-three-day-old female rats weighing 30 to 40 gm., will produce at autopsy on the fifth day a pair of ovaries weighing 65 mg., which is 5 times the weight of the ovaries in the uninjected controls. Experiments on gonadotropic hormone by Snyder and associates and in our own clinic demonstrate the great desirability of administering a gonadotropic substance intravenously in order to produce ovulation. The former authors demonstrated that it was exceedingly difficult to produce ovulation in the rabbit early in pregnancy except with large doses of gonadotropic hormone intravenously.

CONCLUSIONS

1. In this series the patients with amenorrhea as a symptom or who were in the premenarchal or postmenopausal age showed neither clinical improvement nor gross or histologic changes of the tissue.

2. Eight patients (16 per cent) who had menometrorrhagia as a symptom showed clinical improvement, but the endometrial patterns were those of prolonged estrin effect, and we have not observed cessation of bleeding, the presence of a recent corpus luteum, and a progestational type of endometrium in any of these patients.

3. In patients with regular menses, we found an effect that could be definitely ascribed probably to the injected principles.

4. The anterior pituitary gonadotropic hormone is probably not available in a sufficiently concentrated preparation for general use.

5. In the group, which received pregnancy urine extract, we cannot escape the thought that the changes noticed are more characteristic of the pregnancy cycle than the menstrual cycle.

6. Gonadotropic hormone therapy dosage should be brought up to that of estrin therapy. The clinically effective dose, from these preparations will likely be large repeated injections over a short period, and probably the minimum dose will total about 25,000 R. U.

We have been aided in these studies by liberal supplies of gonadotropic principles made available by the following concerns: Parke, Davis & Co. (antuitrin-S and antuitrin gonadotropic); Ayerst, McKenna & Harrison (A. P. L., maturity factor, Danish anterior pituitary-like gonadotropic principle; Danish serum gonadotropic principle) and E. R. Squibb & Son (follutin). A part of the expenses of these studies has been defrayed by a grant from the Research Council of Duke University.

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a spill of sugar into the urine occurs at a relatively low blood sugar level, but if the sugar tolerance is high, such a spill occurs only at much higher levels. The factor regulating the bleeding spill of the endometrium is quite certainly the quantitative hormonal interrelationship between the ovaries and the pituitary.

We have been somewhat encouraged by our experience with the gonadotropic preparation made from the blood serum of pregnant mares, the same preparation as that which Dr. Ross has employed. It is much too early to speak of the results, and we are prepared for later disappointment if it comes. If and when we find it possible to bring about ovulation by endocrine treatment, as I firmly believe we shall be able to do in the not very distant future, an enormous advance will have been made, not only in the treatment of anovulatory sterility, but also of the common type of functional bleeding, which is likewise dependent primarily upon a failure of ovulation.

DR. KARL H. MARTZLOFF, PORTLAND, OREGON.—Dr. Ross mentioned the importance of obtaining endometrial biopsies. Will he please describe briefly in closing what biopsy technic was used in his study?

DR. J. L. FRAENKEL, NEW YORK CITY (BRESLAU).—The normal effects of the hormones develop and regress. If the corpus luteum persists, there develops a pathologic condition. The gonadotropic hormones cause the development of many follicles simultaneously in the lower animals and many corpora lutea develop. The ovary becomes full of them and they may regress slowly—in rats not for five months. One can thus produce sterilization in place of stimulation. Hence one must be very careful in his therapy, and should use the hormones therapeutically, only in small doses and not over a long time.

DR. ROSS (closing).—We resort to frequent endometrial biopsies to aid in the diagnosis of anovulatory bleeding and to determine evidence of progestational response. It so happens that we use the Burch forceps technic, though Dr. Novak's suction curette would answer the purpose equally as well. We take into consideration the work of Bartelmez and endeavor to explain progestational reaction of the endometrium when it is found.

If a portion of the ovary cannot be obtained, we have the significant areas drawn at laparotomy. If a portion of the ovary is obtained, we select that area which is more likely to show partial evidence. It is photographed in the gross under a dissecting microscope and under low power.

A study of our tables will show a duplication of some of the findings which Dr. Davis has described. Where we have a regular cycle, we are likely to find evidence which may be interpreted as an exaggerated gonadotropic effect. We consider the presence of a progestational reaction of the endometrium and the presence of a recent corpus luteum in the ovary of a patient who has been proved to have an anovulatory state as evidence of gonadotropic effect. The best test for these substances is found in this type of patient.

We administered gonadotropic hormone from mare serum intravenously in varying doses to over 50 women who were to be subjected to laparotomy for a variety of pathologic conditions. We varied the time interval so that we could learn the effect of this substance at various times in the cycle. Before the substance was administered the patient was carefully skin-tested to avoid the possibility of an anaphylactic reaction and we have had no undesirable effects. At the time of operation one or both ovaries were removed along with the diseased process. Although most of our patients were at or near the menopause and their pelvic genitalia distinctly abnormal, nevertheless the results of this study were gratifying. We found that ovulation had occurred in about one-half of the patients injected. In a number of patients two and even three ovulations were present. It may be of interest to note the fact that most of the fresh ovulations occurred between the fifth and the twelfth day and the seventeenth and the twenty-third day of the cycle. In three patients who had no regular cyclical bleeding but metrorrhagia and in whom the endometria showed no evidence of proliferation or secretion, recent ovulations were present. Furthermore, in three patients who had a glandular hyperplasia of the endometrium no ovulation could be produced.

In addition to ovulation, the most characteristic finding in the ovaries was follicle growth and some luteinization, the former being more pronounced than the latter. As Ross and Hamblen have indicated in their paper, the gross appearance of corpora lutea does not often reveal their age. It is necessary to obtain histologic sections to determine this point. These artificial corpora lutea appear histologically to resemble those produced physiologically. It is surprising, however, how few illustrations of very early corpora lutea, hours old, appear in the literature. We will publish a comprehensive study of the development of the corpus luteum in the near future.

Another interesting observation is the rapidity with which ovulation occurs as a result of this artificial stimulus. In the majority of our cases, ovaries removed eighteen to thirty-six hours following the administration of the gonadotropic substance show ovulation. This fact fits in very well with what has been observed in experimental animals.

DR. EMIL NOVAK, BALTIMORE, Md.—When dealing with disturbances of ovulation, we are faced with our ignorance of the hormone factors responsible for ovulation. The best evidence is that rupture of the follicle is brought about by a delicate quantitative balance between the follicle-ripening and luteinizing principles of the pituitary. As this balance is evidently an individual one for different individuals, Dr. Ross' negative results are not surprising, especially since there can be no certainty as to the purely gonadotropic effects of the preparations available for use.

In our very first paper on the employment of the pregnancy urine principles in the treatment of functional uterine bleeding, we emphasized the fact that the good results frequently observed could scarcely be due to the production of luteinization in the ovary. Later we had frequent opportunity of studying both the ovaries and the endometrium of patients so treated, and this confirmed our belief as to the almost complete absence of histologic changes, even though the bleeding would often be checked. Since then many others have made similar observations. The conclusion which I have drawn from this, as well as from other clinical observations, is that histologic changes are no criterion of the bleeding capacities of an endometrium. Either excessive bleeding or complete amenorrhea may be associated with almost any type of endometrium. Hyperplasia, for example, represents only a maximum growth effect of estrone upon the particular endometrium in question, but such an endometrium does not necessarily bleed, for the "bleeding level" of different endometria differs just as does the sugar tolerance of different individuals. In some



Fig. 1.—Follicle cyst.

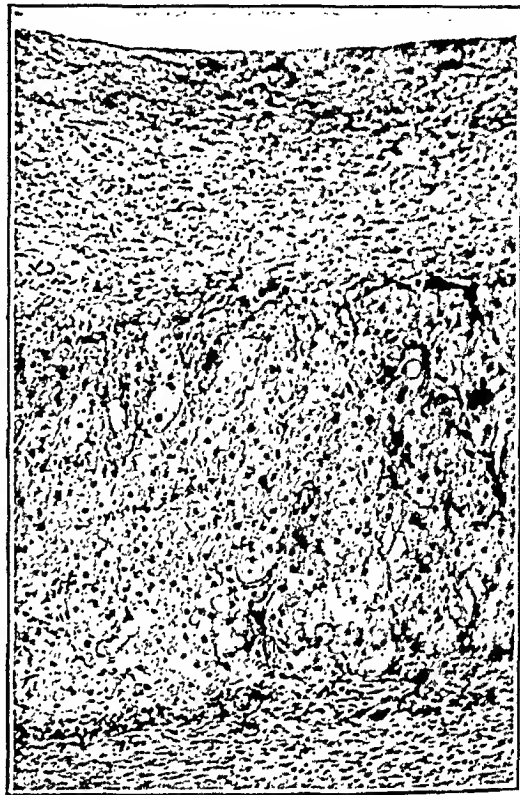


Fig. 2.—Corpus luteum cyst.

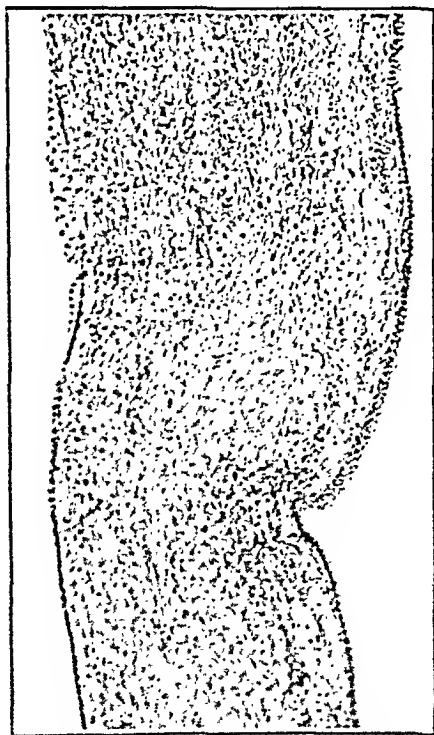


Fig. 3.—Simple serous cyst.



Fig. 4.—Papillary serous cyst.

A STUDY OF THE HORMONAL CONTENT OF OVARIAN CYST FLUIDS*

FRED L. ADAIR, M.D., AND RUTH M. WATTS, PH.D., CHICAGO, ILL.

(From the Department of Obstetrics and Gynecology, University of Chicago, and Lying-In Hospital)

THE purpose of this investigation has been to determine the presence of and variation in the concentration of the estrogenic hormone in the fluid content of various types of genital cysts and to discover the relationship between the hormone and the secretory cells of the cysts.

A study has been made of 229 fluids from various types of adnexal cystic tumors and an attempt made to correlate the estrogenic hormonal content with the histologic findings.

Among those workers who have reported observations of the estrogenic hormone content of cyst fluids, Moulouguet and later Philipp have tried to correlate the hormonal content with the histology of the cysts.

The classification of ovarian tumors is notoriously unsatisfactory and unscientific, and we are not attempting to establish one, but for the purpose of clarity it has been necessary to adopt one which was adapted to our present needs. The following classification will be used for this report:

TABLE I. CLASSIFICATION OF CYSTIC ADNEXAL TUMORS

Ovarian cysts (97)	
Single type (76)	
Follicle (13)	Fig. 1
Corpus luteum (10)	Fig. 2
Simple serous (26)	Fig. 3
Papillary serous (6)	Fig. 4
Papillary pseudomucinous (15)	Fig. 5
Dermoid (2)	
Miscellaneous (4)	Figs. 6, 7, 8, 9
Multiple type (12)	Fig. 10
Bilateral type (9)	
Ovarian cysts associated with malignancy (8)	Figs. 11, 12
Ovarian cysts associated with pregnancy (16)	Fig. 13
Embryologic rests (8)	Fig. 14
Endometrial-like rests (3)	
Inflammatory (2)	
Cystic fibromyomas (2)	

The accompanying illustrations will give the reader an idea of the morphology of each type. It was not possible to fit each and every tumor into an exact pigeonhole, but this was done as accurately as possible by their gross and minute morphology.

*Read at the Sixty-Second Annual Meeting of the American Gynecological Society, held at Swampscott, Mass., May 31 to June 2, 1937.

This work has been done under a grant from the Douglas Smith Foundation for Medical Research of The University of Chicago.

The bilateral group includes cases in which the cysts present on both sides were either single- or multiple-type cysts.

Separate consideration is given to malignant cystic tumors and to those cysts which were associated with a pregnancy.

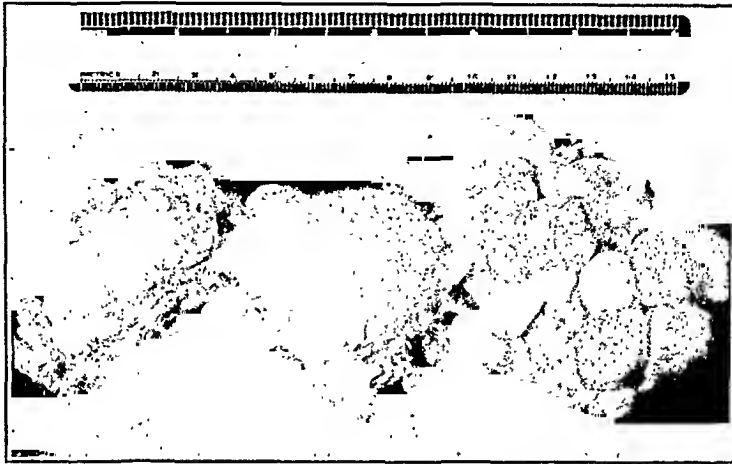


Fig. 8.—Multiple bilateral cysts.

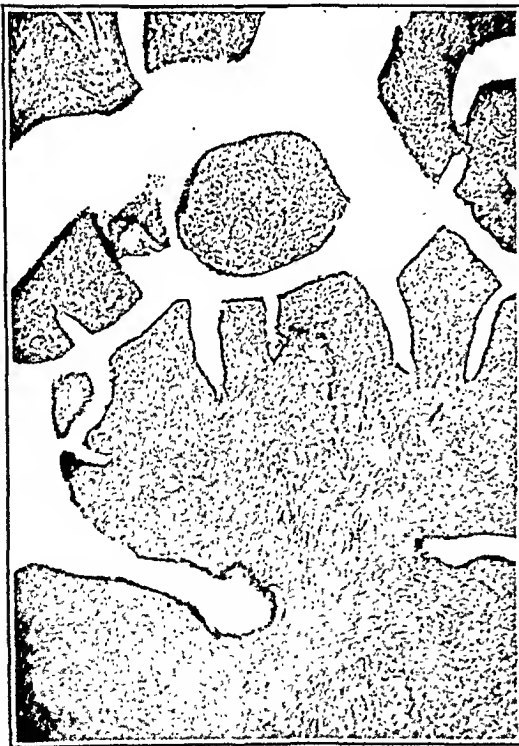


Fig. 9.—Microscopic appearance of multiple bilateral cysts.

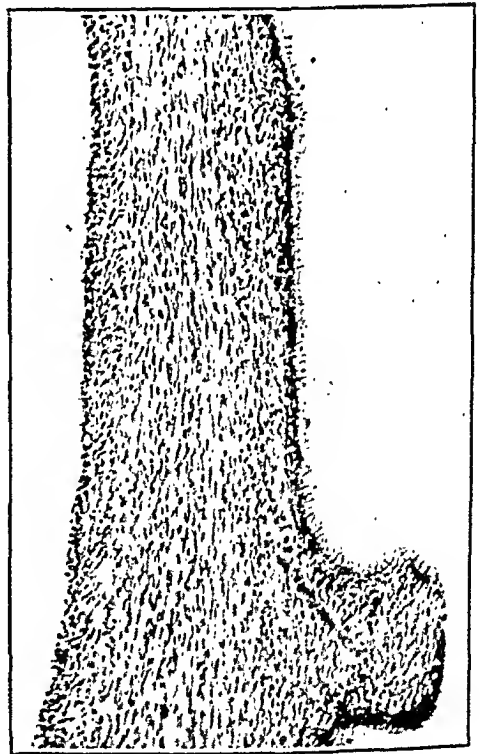


Fig. 10.—Multiple type ovarian cyst.

The nonovarian group includes those cystic neoplasms which were thought to arise from embryologic rests, from endometrial-like tissue, and from inflammatory processes and cystic fibromyomas.

The present report is based on an investigation of 158 cases of cystic genital tumors in which a histologic study and an estrogenic hormone analysis have been run in parallel.

One must recognize those tumors which are derived from ovarian tissue and those which are not, those which arise from secretory types of cells and those which do not.



Fig. 5.—Papillary pseudomucinous cyst.



Fig. 6.—Granulosa cell cyst.



Fig. 7.—Cyst with cholesterol crystals.

Cysts are not always single, but they usually are—this type includes those unilateral tumors of one type from which one type of fluid was obtained.

The multiple type includes unilateral ovarian cysts representing more than one type of cyst and more than one type of fluid.

The cyst fluids have been tested for estrogenic hormone in castrated adult rats. Vaginal cornification has been used as the criterion of a positive test. The fluids have been administered either without extraction in 3 doses (in one day) or in one dose in oil after they had been concentrated by the alcohol and ether extraction method.* The maximum dose was equivalent to 200 c.c. of fluid or less, depending upon the size of

TABLE II. OCCURRENCE OF ESTROGENIC HORMONE IN CYSTIC ADNEXAL TUMORS

OBSERVER	NO.	TYPE OF CYST	AMOUNT FLUID TEST- ED (C.C.)	HORMONE	
				+	-
Moulonguet, Frank, Burch, Kleine, Philipp	12	Follicle	1-5	11	17
Moulonguet, Frank, Kleine, Philipp, Geist, Probstner	12	Corpus luteum	0.5-4	8	4
Frank, Philipp	18	Simple serous	1, 3	1	17
Frank, Kleine, Philipp	> 3	Papillary	3	0	> 3
Frank, Kleine, Philipp	> 8	Pseudomucinous	1.5, 3	1	> 7
Kleine, Philipp	> 3	Dermoid	1.5, 3	1	> 2
Wagner	1	Granulosa	0.3	1	0
Philipp	1	Necrotic	3	1	0
Moulonguet, Kleine, Bis- kind	7	Unclassified	1.5-15 (?)	5	2
Moulonguet, Philipp	3	Corpus luteum, pregnancy	0.5, 3	1	2
Philipp	1	Serous, pregnancy	3	1	0
Philipp	1	Pseudomucinous, preg- nancy	3	1	0
Probstner	1	Corpus luteum, hydatid mole	?	1	0
Kleine	1	Carcinoma	1.5	0	1
Philipp	5	Chocolate	3	0	5
Philipp	2	Adnexal	3	0	2
Moulonguet, Dierks, Frank, Kleine, Philipp	> 12	Embryologic	1-3	0	> 12
Philipp	1	Parovarian, pregnancy	3	1	0

the cyst. Extractions were made in triplicate wherever the quantity of material permitted. An attempt has been made to estimate the potency of these fluids, but the limited amount of material precludes an accurate assay of most fluids.

The work summarizes nearly 2,000 tests for estrogenic hormone and approximately 600 extractions of cyst fluid.

There is a condensed summary of the work reported in the literature shown in Table II. Other reports have been omitted because the methods used did not preclude the effects of gonad-stimulating hormones. This table shows a total of 92 cysts of which 65 are ovarian, 20 non-ovarian, and 7 complicated by pregnancy or malignancy.

*Two volumes of 95 per cent alcohol were added slowly to one volume of cyst fluid. After standing overnight at room temperature the mixture was centrifuged. The supernatant fluid was decanted through a Jena glass filter. The residue was triturated twice with 95 per cent alcohol and once with ether. The supernatant fluid and the washings were combined and made acid to Congo red with hydrochloric acid. The solution was evaporated to dryness under reduced pressure. The residue was triturated with four 25 c.c. portions of anhydrous ether. The ether solution was added to a known quantity of olive oil and the ether removed.

The tissue specimens have been prepared by formalin and celloidin technic, stained with hematoxylin-eosin, and classified particularly from the appearance of the lining cells.



Fig. 11.—Ovarian cyst associated with malignancy.

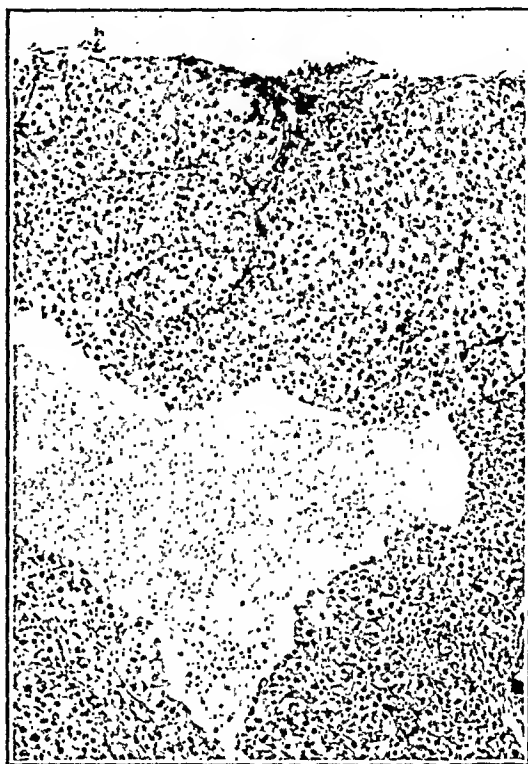


Fig. 12.—Ovarian cyst associated with malignancy.

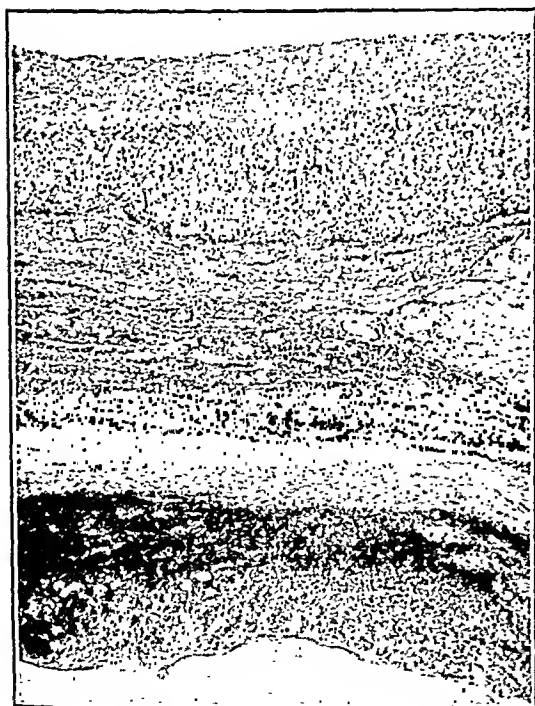


Fig. 13.—Ovarian cyst associated with pregnancy.

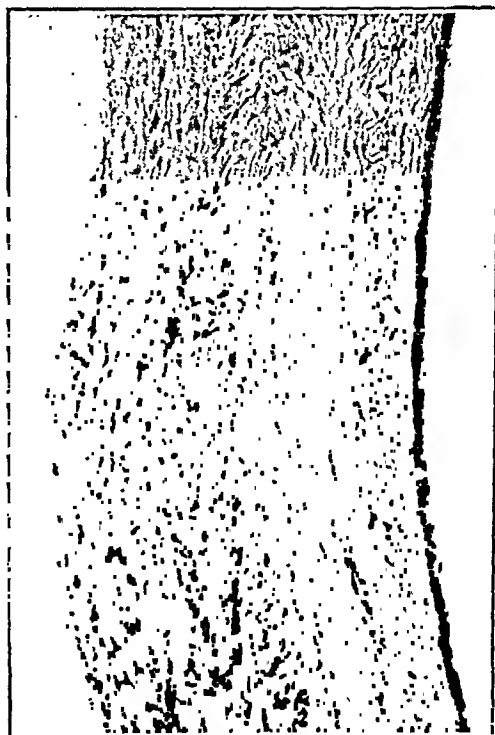


Fig. 14.—Embryonic rests.

The relation between the type of cyst and the presence of the hormone is shown in Chart 3. About 85 per cent of the follicle, 50 per cent of the corpus luteum, 30 per cent each of the simple and the papillary serous, and about 13 per cent of the pseudomucinous cysts exhibited the presence of estrogenic hormone.

In the 8 ovarian cysts associated with malignancy, 3 showed estrogenic hormone and 5 did not.

In the 16 ovarian cysts associated with pregnancy, estrogenic hormone was present in 6 and absent in 10.

The group of cysts in which ovarian tissue was not incorporated includes 8 cysts arising from embryologic rests (parovarian, wolffian.

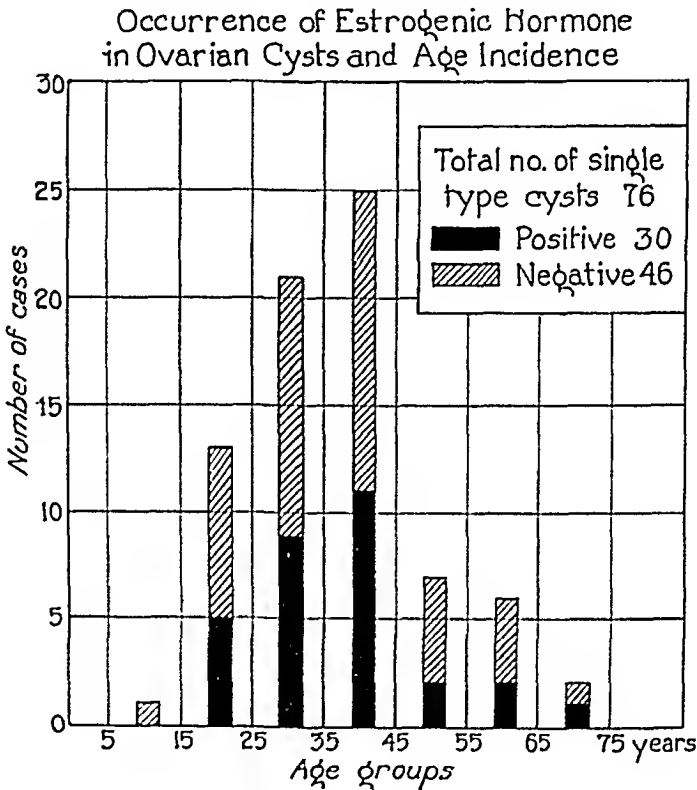


Chart 2.

hydatid), 3 arising from endometrial-like rests (chocolate cysts), 2 inflammatory cysts, and 3 cystic fibromyomas. All of these cyst fluids were negative except 2 parovarian cyst fluids, one of which was associated with pregnancy.

An attempt has been made to evaluate the significance of the presence of the estrogenic hormone in the different types of cysts by its frequency of occurrence and its potency. These findings are shown graphically in Charts 4 to 7.

Chart 4 gives a summary of 143 cyst fluids excluding those cysts which were associated with pregnancy and malignancy. The fluids have been arranged according to the type of cyst, as shown on the left

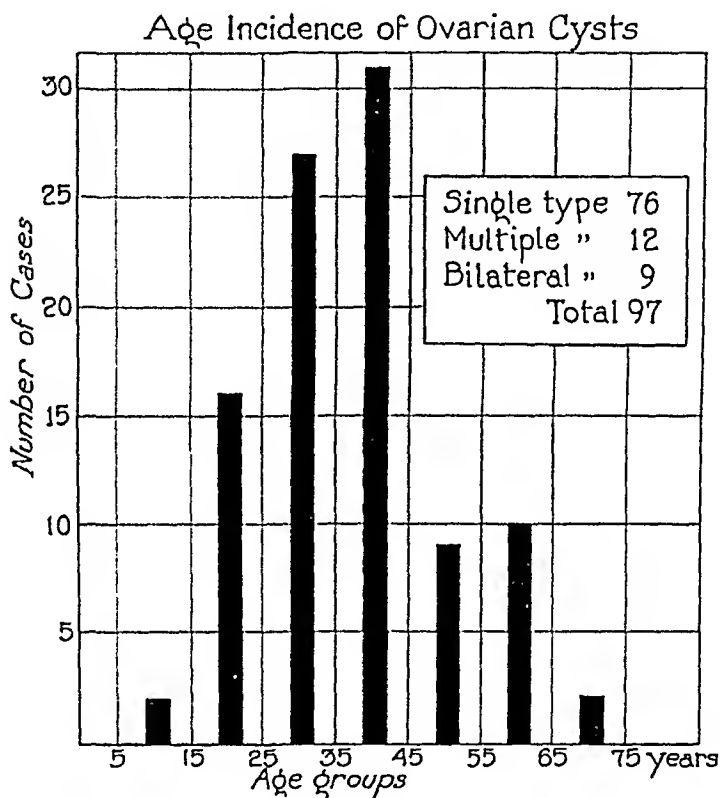
These reports indicate that all positive cases, with the exception of one parovarian cyst associated with pregnancy, are in the ovarian group.

It is to be noted that with one exception small quantities (0.5 to 3 c.c.) of fluid were used.

In some of our cases as much as 200 c.c. of cystic fluid was used for the test.

Our cases have been analyzed from various points of view.

The age incidence in the series of 97 ovarian cysts unassociated with pregnancy or malignancy is shown in Chart 1. Most of these cysts appeared during the age of ovarian activity, 76 per cent occurring



between the ages of fifteen and forty-five years, and 32 per cent between the ages of thirty-five and forty-five years. About 2 per cent occurred under fifteen years and approximately 22 per cent after forty-five.

The occurrence of the estrogenic hormone and age incidence are shown in Chart 2. In this chart 76 single type-cysts are shown.

Twenty-five of 30 positive tests occurred in cysts between ages of fifteen and forty-five years, which corresponds closely to the percentage of cysts in this age group. Twenty-five positive tests occurred in 59 cases, or about 42 per cent, while 5 positive tests, or 33 per cent, occurred in those patients beyond forty-five years of age. It is noteworthy that estrogenic hormone was present in such a large percentage of cases beyond the age of forty-five years.

amount of fluid tested for each cyst. The dots show fluids in which hormone was found, and the position of the dot shows the minimum dose at which it gave a positive test. The circles denote negative fluids, and the position of the circle indicates the maximum dose at which it was tested. At that dose either the material was exhausted or a dose equivalent to 200 c.c. of fluid had been given. For example, three follicle cysts were positive at as low a dose as 0.03 c.c., but another follicle cyst was negative at as high a dose as 25 c.c. In general, the negative values are found at dose levels equal to or greater than those at which hormone has been found in similar fluids (e.g., in the follicle and corpus luteum

Occurrence of Estrogenic Hormone in Relation to Size of Ovarian Cysts

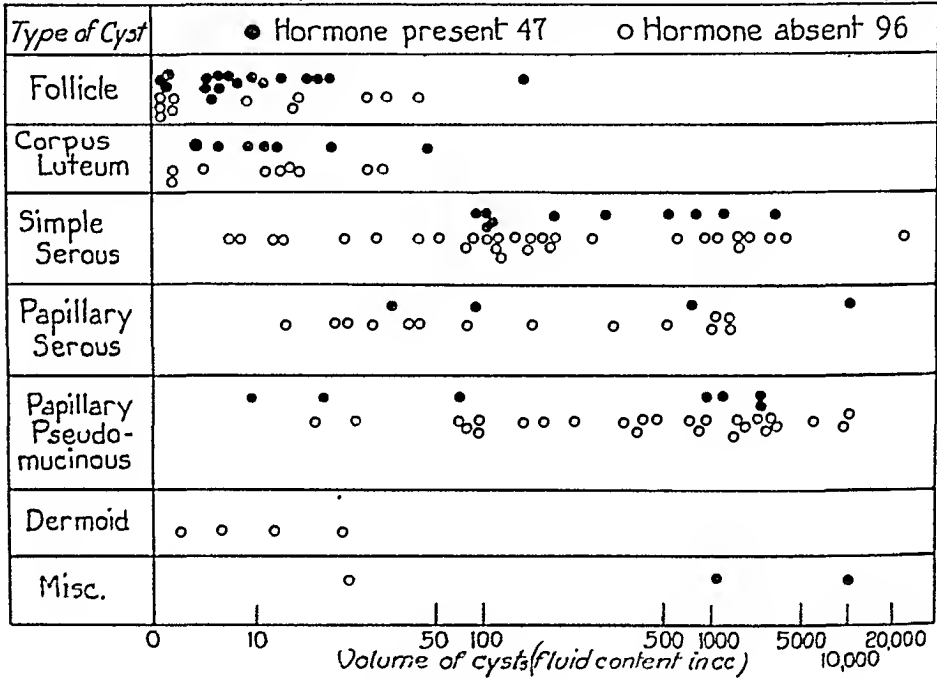


Chart 5.

groups). The chart is a summary of approximately 1,000 tests and 350 extractions. Forty-seven fluids were positive and 96 were negative.

The measured fluid content of cysts is given in Chart 5, and the variation in the presence or absence of hormone is shown. The type of cyst is shown on the left margin. The size of the cyst, in terms of the amount of fluid obtained, is shown on the base scale, which is greatly compressed because of the wide range in size (cysts as large as 22,000 c.c.). The circles and dots represent single fluids. The dots merely indicate fluids which contained hormone, and the circles, fluids which were negative. The dose levels were those shown on the previous figure. The hormone occurs in the large as well as in the small cysts, and, conversely, many small cysts are negative. It would seem that size of the cyst is not an important factor in the occurrence of hormone.

DISCUSSION

DR. EDWARD D. ALLEN, CHICAGO, ILL.—The most interesting point to me is Dr. Adair's finding that the endometrial cysts do not give a positive test for estrogenic hormone. We already know that the ectopic endometrium of endometriosis is responsive to hormonal change in menstruation and pregnancy and also that the menstrual blood shed from the normal uterus is high in estrogenic content.

To illustrate certain points about endometriosis, section is shown of a corpus luteum which has very definite endometrial glands far out in the lutein layer. The production of cells from the ovarian stroma is perhaps only two weeks old, so that the same stimulus has probably caused the functional growth of the lutein cells as well as this epithelium which forms typical endometrial-like glands. Whether it is the pituitary that controls this follicular stimulation or not remains to be seen. Certainly the fact that the cells in these glands are histologically perfect makes us wonder if they could possibly have been implanted, or whether they are part of a metaplasia or hyperplasia from the ovarian stroma.

DR. C. FREDERIC FLUHMAN, SAN FRANCISCO, CALIF.—From our present knowledge some of Dr. Adair's findings were predictable. For instance, the larger amounts found in follicle and corpus luteum cysts are in keeping with our belief that granulosa and theca cells are concerned with the production of estrogen. The occurrence of estrogenic hormone in cysts in women over forty-five years of age is understandable in view of its previous demonstration in the blood and urine of such patients. I should like to ask Dr. Adair if in cases with multiple cysts the amounts of hormone in the various cysts were comparable?

As a possible explanation for variations in the amount of estrogen present in cyst fluid, I should like to suggest the possibility that the stage of the menstrual cycle at which the specimen was obtained may be of importance. It is not inconceivable that an increase may occur at the time when blood and urine normally show a rise.

DR. J. L. FRAENKEL, NEW YORK CITY (BRESLAU).—One might question whether the ovarian cysts which are occasionally seen in the newborn bring about changes in the uterus and vagina. I formerly found enormous quantities of giant cells in vaginal smears of the newborn which after about four weeks disappear. The epithelium of the older child is low, 5 to 6 cell layers deep, but in the newborn 30 to 40 cell layers deep, with 10 to 20 cell layers being cast off like the spongiosa layer of the decidua.

The witch's milk is present on the day of birth, even in prematures, and is especially frequent in negroes. Dr. Thales Martins and I have demonstrated a greater swelling of the uterus in mice that had been injected with this milk than with mother's milk. (One must extract the milk with ether, otherwise the animals die.) Thus this is not an estrogenic hormone but probably gonadotropic.

DR. EMIL NOVAK, BALTIMORE, MD.—The results of this study are about what one would expect if one takes into account the histogenesis of the various types of ovarian cyst and the assumed rôle of the living cells in the production of estrone. Normally the latter has its chief ovarian source in the follicle epithelium and probably also the theca cells, so that it is not surprising that follicle cysts are likely to be most constant and richest in their estrogenic content. The same statement may be made concerning corpus luteum cysts.

The histologic appearance of any tissue is, however, not always a good criterion of its functional activity. One of the best illustrations of this statement is to be found in the case of so-called cystic ovaries, in which the ovaries are full of many small follicular cysts. As a rule these tiny cysts represent follicles in various stages of atresia, some with epithelium still present, others in which both the ovum

scale. Dots and circles represent individual fluids. The "units" are based on the lowest positive dose, as on the previous chart. The dots represent positive fluids, and the circles represent negative fluids, that is, those which contain less than the number of "units" designated on the scale. The positive fluids range in potency from 0.005 "unit" per c.c. (i.e., a dose of the equivalent to 200 c.c. of fluid was positive) to 33 "units" per c.c. (i.e., a dose of 0.03 c.c. was positive). This range is equal to a range of 5 "units" per liter to 33,000 "units" per liter. Probably potency values below 0.05 "unit" per c.c. (i.e., the equivalent of 50 "units" per liter) are those that might be anticipated in general body fluids and tissues and are, therefore, of little significance here. Seventy-seven per cent of the positive fluids have a potency greater than 0.05 "unit" per c.c. or 50 "units" per liter. Within the group of positive fluids, fluids of different types seem to show a somewhat characteristic range of potency. Positive follicle fluids range from 0.1 "unit" per c.c. to 33 "units" per c.c. Positive corpus luteum fluids range from 0.2 "unit" per c.c. to 1.2 "units" per c.c. Positive simple serous fluids show a maximum of 0.12 "unit" per c.c.

A summarization of the findings is shown in Chart 8. The type of fluid tested is shown on the left margin. The fluids are divided into ovarian and nonovarian groups. The number of fluids is represented by the length of the bars. The solid bars show positive fluids, the cross-hatched bars the negative fluids.

Total number of ovarian fluids: 54 positive (33 per cent); 109 negative

Total number of ovarian fluids associated with malignancy: 3 positive; 5 negative

Total number of ovarian fluids associated with pregnancy: 6 positive; 10 negative

Total number of nonovarian cyst fluids: 1 positive; 18 negative

Ascitic fluids: 1 positive; 19 negative

Twenty-one cyst fluids tested for gonadotropic hormone were negative at the dose levels tested, except in special cases.

An attempt to correlate the presence of the estrogenic hormone with the menstrual cycle revealed no results which warrant conclusions at this time.

CONCLUSIONS

In some ovarian cyst fluids estrogenic hormone would seem to be found in sufficient amount to be considered of intrinsic origin, but in others in amounts which might be anticipated in body fluids in general, i.e., extrinsic.

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AN EFFICIENT COMPOSITE OPERATION FOR UTERINE PROLAPSE AND ASSOCIATED PATHOLOGY*

EDWARD H. RICHARDSON, M.D., BALTIMORE, MD.

(From the Department of Gynecology of the Johns Hopkins University and Hospital)

THE more advanced grades of uterine prolapse are commonly encountered in association with hypertrophy, elongation and chronic infection of the cervix, benign disease of the corpus, pronounced descent of the bladder or cystocele, impairment of the vesical sphincter, urethrocele, a broken-down perineum and pelvic floor, rectocele and enterocele. Successful management of such complex vaginal hernias often taxes to the utmost the skill and resourcefulness of even the most experienced pelvic surgeons, for no single plan of reconstructive surgery has yet been devised which is rationally applicable either to all types or to the several age groups. Consequently, if an attempt is made to treat indiscriminately a considerable number of them according to any single stereotyped operative procedure, it will inevitably result in a disappointing percentage of only partial successes and not a few outright failures. Uniformly good end-results will be obtained only through the utilization of a comprehensive therapeutic program: one which includes first, intelligent preoperative study and preparation of the individual patient; second, the exercise of discriminating judgment in the choice of operation to be employed; and, third, diligent and enlightened postoperative care.

From the standpoint of surgical therapy alone, all patients afflicted with vaginal hernias fall naturally into two age groups; young women in whom the partial or total preservation of function is highly desirable, and older women in whom this factor becomes one of subordinate importance. A substantial majority of the advanced grade cases are encountered in the menopausal years, representing as they do the terminal consequences of repeated childbirth trauma, sustained hard work, and progressive atrophy of supporting structures. On the other hand, the lower age group, recruited in part from those whose muscular and fascial supports are congenitally defective but composed chiefly of those unfortunates who have been the victims of both economic pinch and mediocre obstetric care, are encountered altogether too frequently in every clinic. Preservation of function in these younger women always involves a decision regarding continuation of menstruation, sexual relations, and further childbearing. In arriving at this decision due consideration must be given not only to the extent of damage which the

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and epithelium have degenerated. Such cysts would be expected to show little or no estrone activity. By contrast, in some cases of hyperplasia of the endometrium associated with functional bleeding, one may see ovaries which grossly are quite similar, but in which the granulosa and often the ova are well preserved. In this latter group one may expect to find a high degree of estrogenic activity.

In still other types of follicle cysts, usually multiple, the estrogenic activity merely reflects a relatively high degree of pituitary effect. For example, in the frequently observed cystic degeneration of conserved ovarian fragments left after resection of the ovaries, the pituitary effect seems to be concentrated on a much lessened ovarian registering board, with excessive follicle maturation in such ovarian fragments, in accordance with Lipschultz's "law of follicular constancy." This pathologic-physiologic change is probably much more frequently responsible for cystic degeneration of residual ovarian fragments than is the commonly assumed disturbance of circulation.

DR. ADAIR (closing).—The only conclusion that we felt justified in drawing was that some of these cysts apparently produced their own estrogenic hormone, and others contained an amount of estrogenic hormone which might be considered to be common to the tissues in general. With few exceptions, the cysts which we thought were not associated with ovarian tissue showed no estrogenic hormone, or at least none in high concentration.

We analyzed some of the simple type of cysts with reference to what we called the menstrual age of the cyst, that is, the time of removal in relation to the menstrual cycle. We were not able to see any relationship between the presence of the estrogenic hormone and the menstrual cycle. We do not like to draw final conclusions because our group of cases was hardly sufficient.

With reference to the presence of hormone in the multiple type of cysts, we did find variations in concentration of the estrogenic hormone. It is, however, not impossible for the fluid of one cyst to diffuse into the fluid of another. It might thus be impossible to tell about the actual source of the hormone in any given fluid.

they should be resorted to only in the poor surgical risk group or when there is scant likelihood of success in attempting to achieve a more normal anatomic reconstruction.

Because of uniformly satisfactory end-results obtained in private patients, my own preference for a number of years was total vaginal hysterectomy. But recent follow-up studies conducted in Dr. Cullen's clinic at the Johns Hopkins Hospital by Everett revealed the surprising fact that total vaginal hysterectomy performed by a group of experienced gynecologists for the treatment of advanced grade vaginal hernias failed to achieve complete anatomic success in 30 per cent of the cases, whereas only 4 per cent of failures occurred following the interposition operation.

But utilization of the Watkins, the Curtis, or the Manchester operation is restricted by reason of the fact that all three presuppose the existence of a normal corpus uteri which, unfortunately, is by no means always present since one frequently encounters instances of uterine prolapse in which associated pathology of the corpus demands its removal. Furthermore, even when an operation of this type may be rationally employed it must be admitted that an interposed normal uterus remains a potential focus of both benign and malignant disease, subsequent treatment of which either by surgical extirpation or irradiation involves extraordinary technical difficulties as well as greatly increased hazard of serious complications and sequelae.

It seemed to me conspicuously worth while, therefore, to construct a composite operative plan that would combine the essential features of total vaginal hysterectomy with those of the several transposition methods and at the same time would eliminate the humiliating percentage of partial failures chargeable to the former procedure as well as the potential dangers left lurking in the latter ones.

Such a plan must be comprehensive in scope having for its objective (1) riddance of the hypertrophied and diseased vaginal portion of the cervix; (2) extirpation of the corpus uteri, together with the tubes and ovaries if indicated; (3) optional destruction or excision of any remaining cervical canal epithelium; (4) minimal trauma and devitalization of structures later to be utilized for reconstruction purposes; (5) preservation of an assured and adequate blood supply to these several units; (6) total ablation of associated enterocele through high obliteration of the culdesac of Douglas; (7) rational utilization of all supporting structures that experience has demonstrated to be helpful and dependable; namely, the pubocervical fascia, the basal portions of the broad ligaments with their extraordinarily strong cervical attachments, the uterosacral and the round ligaments, the fascia of the rectovaginal septum, as well as the muscles and fascial layers of the pelvic floor and perineum; (8) reestablishment of a vagina of normal depth and caliber; and (9) restoration of normal anatomic relationships.

reproductive units and adjacent structures have suffered in consequence of trauma and associated disease but also to the individual patient's general physical condition. Other factors, too, of scarcely less importance include her social and economic status, the number of living children and the hazards of previous pregnancies and confinements.

The operations commonly employed in this younger age group include the application of conservative therapy to a damaged and infected cervix, plastic repair of the fascial bladder and urethral support often including also plication of the vesical sphincter, reconstruction of the pelvic floor, and rectovaginal septum, together with an efficient suspension of the uterus by the abdominal route. The question of permanent sterilization by resection of the uterine ends of the fallopian tubes in these women is always a pertinent and individualistic one to be decided only through judicious examination of the several factors involved. But the surgical problems presented by this group are relatively simple and the reconstructive operations required are not difficult to execute.

Much more complex by contrast are the problems with which the pelvic surgeon is confronted in the advanced stages of vaginal hernias so frequently encountered in elderly women. Collective experience has abundantly demonstrated that even simple abdominal operations are far less well borne by these patients than are the most extensive vaginal procedures. This fact, coupled with the inevitable necessity of supplementing any type of abdominal operation by extensive vaginal reconstructive work performed either simultaneously or in two stages, has led to the gradual development and advocacy of a number of excellent plans devised to reestablish adequate and permanent mechanical support for the several anatomic units involved and to eliminate any coexisting pathology.

The operations most widely employed today in the treatment of these hernias in older women are (1) total vaginal hysterectomy, performed according to individual preference for any one of several well-established methods and supplemented by central fusion and anchorage of the ligamentous stumps, high obliteration of the culdesae, reconstruction of the pubocervical and rectovaginal fascial planes and of the pelvic floor; (2) the Watkins-Schauta-Wertheim interposition operation; (3) the Manchester or Fothergill procedures; (4) the Curtis advancement operation; (5) the Neugebauer-Le Fort colpocleisis; and (6) total colpectomy.

Colpocleisis and total colpectomy appear to have grown in favor within recent years and excellent results are reported by those who have had considerable experience in their use. It seems to me, however, that they are applicable by preference only to very old, feeble women afflicted with complete procidentia or with inversion of the vagina following total hysterectomy. So that while these two operations undoubtedly possess distinct merit and have a definite field of usefulness,

tion partial separation of the anterior vaginal wall from the bladder. With the blades closed the scissors are carefully insinuated beneath the vaginal wall exactly at the midpoint of the initial transverse incision, advanced 2 or 3 cm. and the blades then separated. The segment of vaginal wall thus detached is divided along the midline. By alternate repetition of these two maneuvers completion of the vertical limb of the familiar \perp shaped incision to within 1 cm. of the meatus is much more

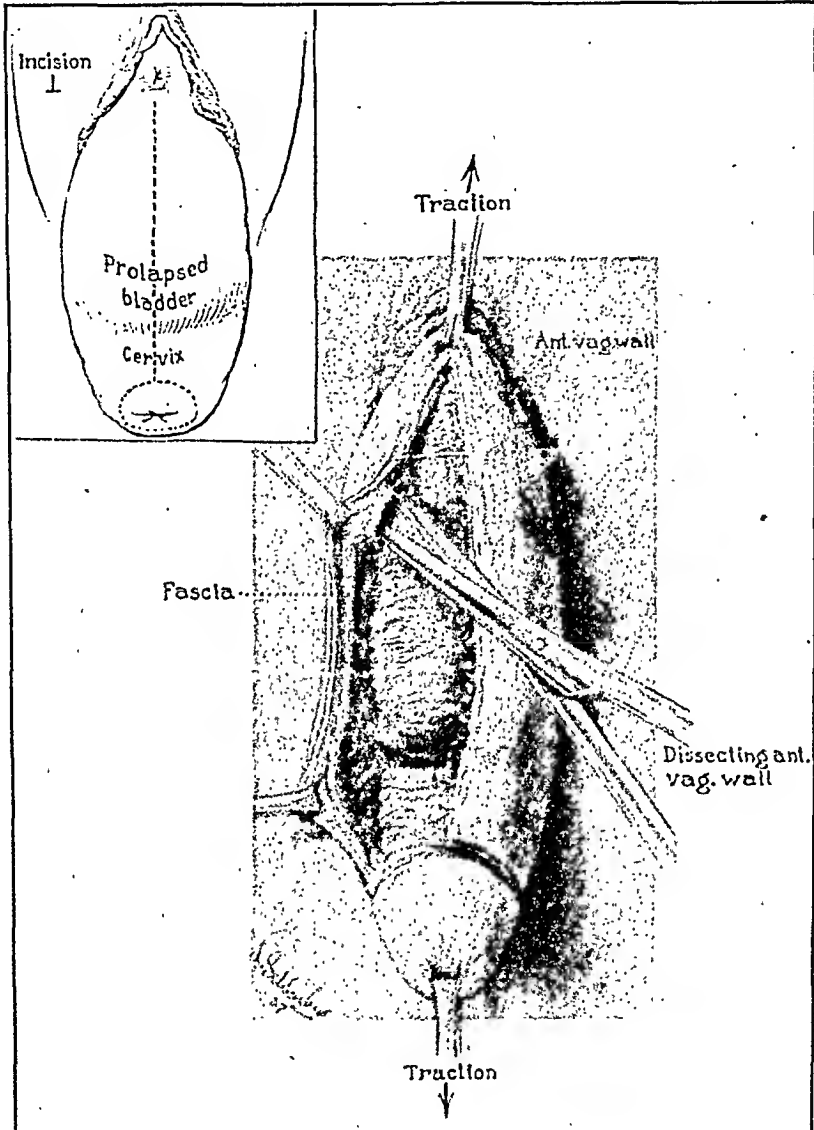


Fig. 1.—Strong traction downward on the protruding elongated cervix and upward on the vaginal wall at a point 1 cm. below the urethral meatus is maintained throughout the dissection here shown. Blunt scissors are being used to separate the bladder from the vaginal wall. The dotted line in the inset indicates the initial inverted T-shaped incision.

quickly executed than by any other method. There is no danger of puncturing the bladder if during this dissection constant traction upon the vaginal wall in opposite directions is maintained so as to obliterate all folds. The plane of cleavage between the bladder and the vaginal wall is easily located and followed.

Step 2: Dissection of the Pubocervical Fascia and of the Bladder.—(Fig. 2.) The two triangular flaps of vaginal wall thus outlined are now successively put under uniform tension by the application to their margins of several Allis clamps. Instead

Now all of these requirements can be adequately met by judicious selection from such well-established vaginal operations as those discussed above, which are widely employed today in the treatment of vaginal hernias, certain of their most dependable features and combining these into a composite reconstructive plan more comprehensive in scope and of greater flexibility and efficiency than any one of the contributing models. In the operation about to be described this is precisely what I have done; consequently, no claim of originality is made in its presentation beyond that involved in the construction of what I believe to be an improved plan out of borrowed units for each one of which I hereby make grateful acknowledgement to the distinguished gynecologists who originally devised them.

One cannot too strongly emphasize the vital importance of adequate preparation of the individual patient through a period of hospitalization sufficiently long to permit completion of a general diagnostic study and the application of such fortifying therapeutic measures as it may indicate. Not uncommonly complete procidentia is associated with vulval dermatitis or other skin diseases, with gravity ulcers, with chronic infection of the cervix or with edema of the prolapsed structures and impairment of circulation. Existence of such maladies is an absolute contraindication to radical operative intervention and they must be absolutely cleared up beforehand by a period of rest in bed and intelligent general and local therapy. So also coexisting cardiovascular embarrassment, renal impairment, diabetes and obesity are frequently encountered and require a period of intensive treatment prior to operation. And, finally, a judicious choice of anesthesia must be made in accordance with the experience and convictions of the individual surgeon.

TECHNIQUE OF THE OPERATION

The Surgical Toilet.—The bladder and rectum must be empty. Scrupulous care and thoroughness must be exercised in the preliminary surgical toilet of the operative field. First, the entire pubic and vulval regions, the adjacent inner surfaces of the thighs and the perianal area must be cleanly shaved. Next a thorough washing externally over a wide circumference is done successively with green soap and warm water liberally applied, 1:1,000 solution of bichloride of mercury and 70 per cent alcohol; then follows an identical cleansing of the vagina and cervix; and, finally, a widespread and accurate application to both the vulva and vagina of Scott's solution (1 per cent acetone; 2 per cent mercurochrome; in 70 per cent alcohol). A folded sterile towel is now anchored over the anus by means of an adhesive strap securely applied across the buttocks. The upper margin of this towel is then sutured to the upper margin of the perineum and the sterile draperies are adjusted.

Step 1: Separation of the Anterior Vaginal Wall From the Bladder.—(Fig. 1.) The cervix is exposed, its anterior lip grasped with a straight Jacobs forceps and strong downward traction is made. An Allis clamp is applied to the vaginal wall in the midline 1 cm. posterior to the urethral meatus and sufficient traction upward is made upon it to flatten out the entire anterior vaginal wall. A transverse incision is now made through the vaginal wall 1 or 2 cm. above the external os and partly encircling the cervix. Straight Mayo scissors are next used to effect by blunt dissec-

ligaments, thus skeletonizing the hypertrophied and elongated portion, often 5 to 10 cm. long, which is then amputated. The cervical canal above this level is next dilated, the vaginal cuff is pared down to proper width, then fitted neatly over the

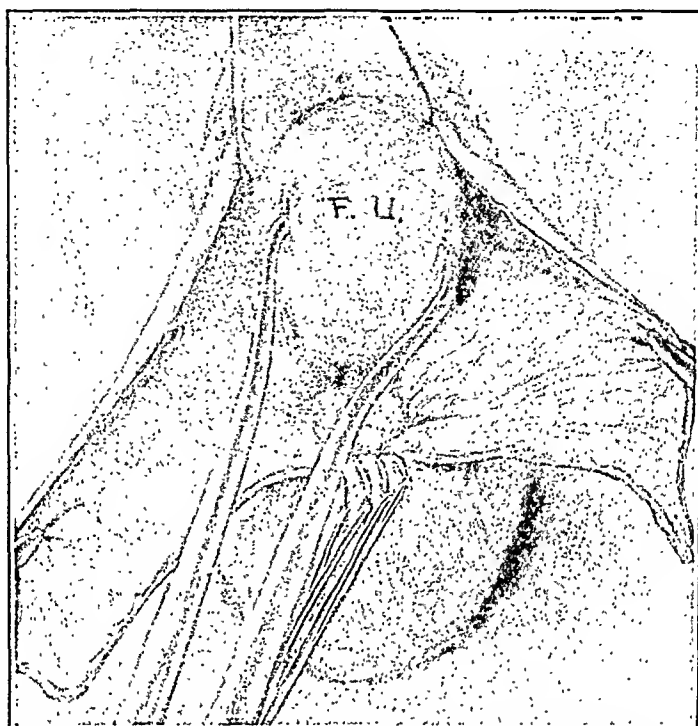


Fig. 3.—The peritoneal cavity has been opened between the uterus and the bladder and the enlarged corpus uteri is being delivered by traction.

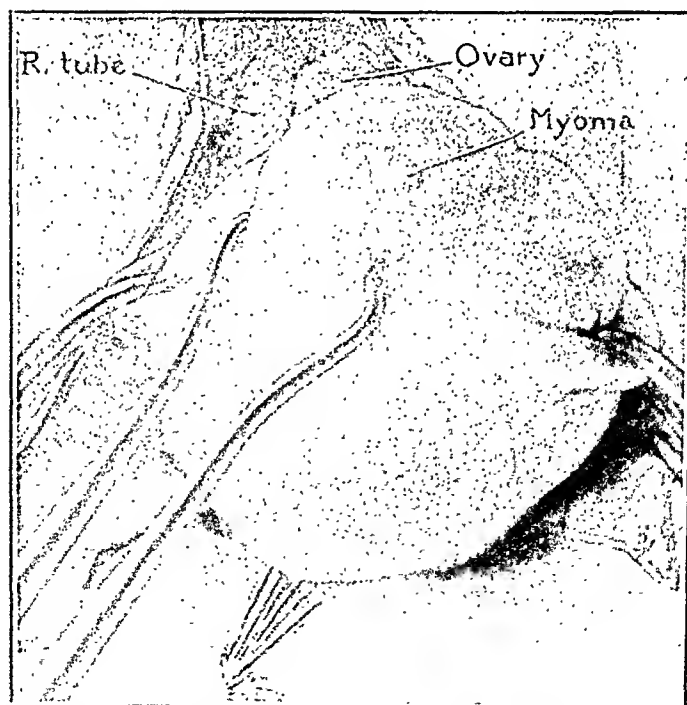


Fig. 4.—The myomatous corpus uteri is shown fully delivered. The right tube and ovary are clearly seen. A single clamp has been applied on each side to the uterine ends of the tube, the round and the uteroovarian ligaments prior to their division.

then of being content simply to separate further the bladder laterally by blunt dissection, it is also possible always to obtain from each flap by careful sharp dissection a substantial and valuable layer of pubocervical fascia. Normally this structure constitutes the chief support of the bladder base and cystocele is essentially a herniation through it. Consequently, it will always be found thin and attenuated over the central zone but supplies a supporting layer of surprising thickness and tensile strength when the dissection is carried well out on each side. It merges above into the two vesico-cervical fascial pillars which, in turn, fuse with the basal segments of the broad liga-

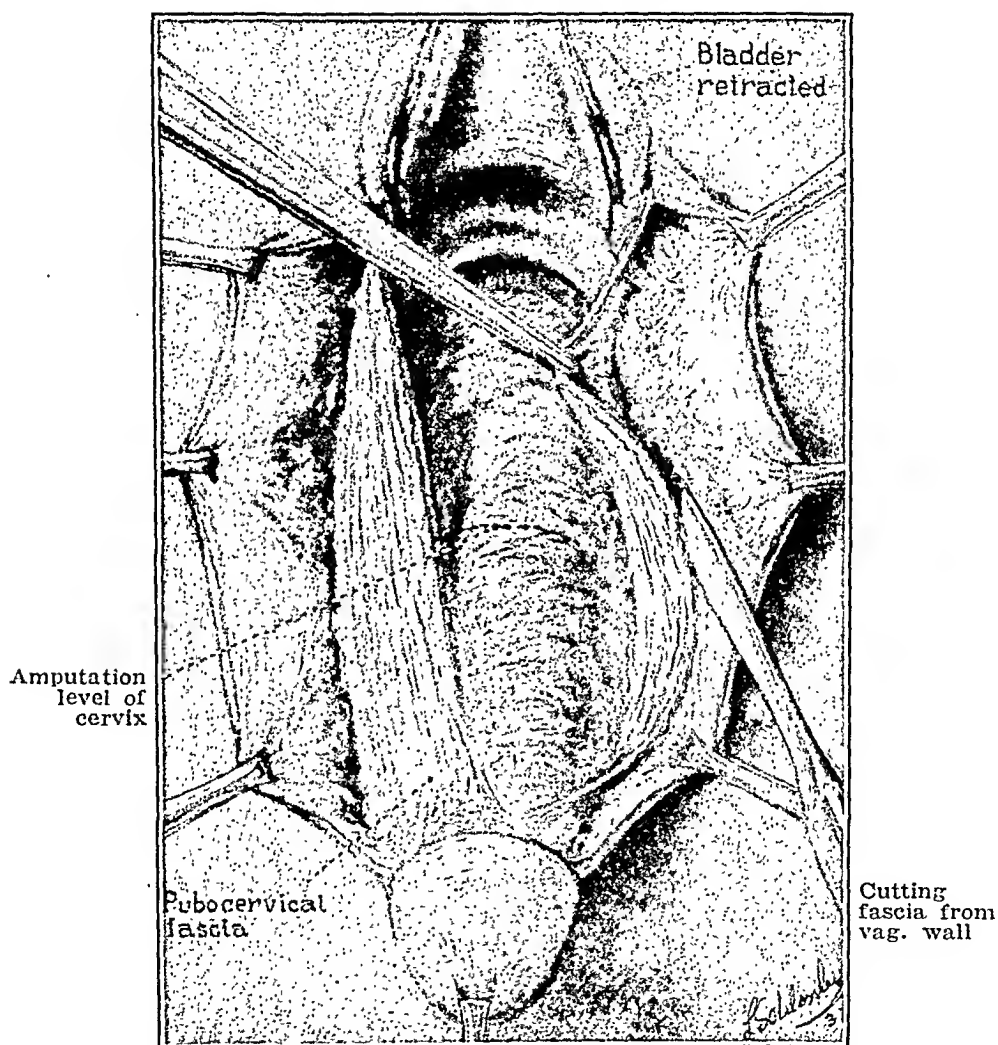


Fig 2.—After completing the separation of the vaginal wall and bladder from the elongated and hypertrophied cervix a guillotine amputation of the latter is done at the level indicated. Preliminary dissection of the pubocervical fascia from the vaginal flaps is here shown.

ments, thus furnishing two remarkably sturdy fascial bands for later approximation and anchorage to the cervical stump as presently to be described. Clean anatomic identification and utilization of this fascia is a step of prime importance in achieving permanent cure of cystocele. The bladder is next separated from the cervix also by blunt dissection initiated with Mayo scissors and continued upward with the index fingers until the vesicouterine peritoneum is freely exposed.

Step 3: Amputation of the Cervix.—The initial transverse incision is now extended to encircle completely the cervix and from the latter the vaginal cuff is quickly stripped off posteriorly and on each side quite up to the bases of the broad

the vagina with far less effort, trauma and hemorrhage than if the sharp pointed forceps shown in the illustrations are used.

Step 5: Removal of the Corpus Uteri.—(Fig. 5.) A subtotal hysterectomy is now done. If the ovaries are to be removed, the infundibulopelvic ligaments are identified, adequately exposed, clamped, divided and doubly ligated with chromic catgut. If the ovaries are to be retained, two clamps are applied on each side across the uterine ends of the fallopian tube, the round and the uteroovarian ligaments between which these structures are amputated as close to the cornua as possible. The clamps on the distal stumps are now replaced by transfixing sutures of chromic catgut which are securely tied around them and left long for later traction usage. The uterine vessels are now clearly visible on each side. They are next clamped at the level of the internal os, divided and doubly ligated with chromic catgut. The cervix is now cut across at this level, being slightly cupped to permit a neater closure of it. Upon removal of the corpus, it is at once laid open for accurate inspection of both the endometrium and the myometrium. If no suspicion of malignant disease is found, the cervical stump may now be safely utilized for supporting purposes. If before

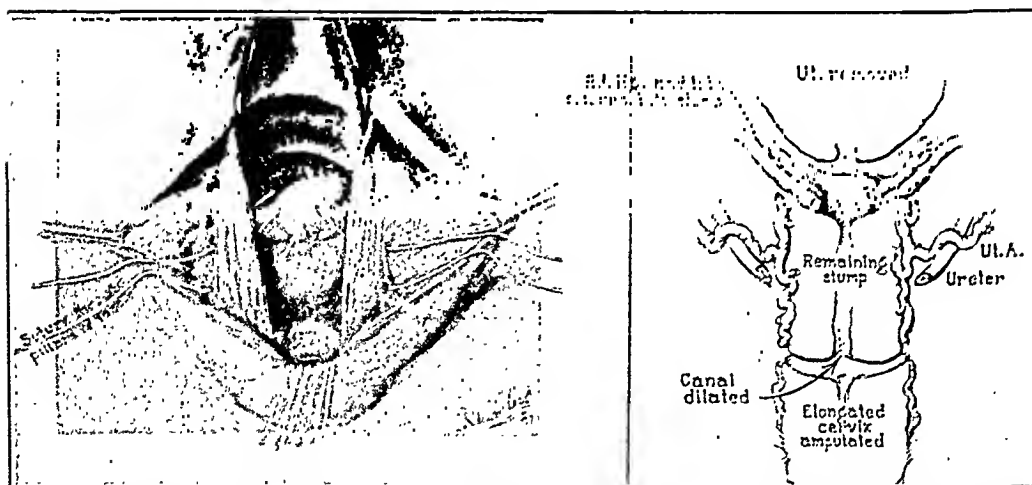


Fig. 6.—Only that segment of the uterus to which is attached on each side its major supporting structure, the basal portion of the broad ligament, remains. This is interposed beneath the bladder and securely anchored by sutures which also include and approximate the stout pillars of pubocervical fascia.

doing so, the operator prefers to get rid of the remaining canal endometrium, this may be accomplished either by cauterization or excision. I do not believe that either is necessary.

Step 6: Utilization of the Round Ligaments for Additional Support of the Cervical Stump.—We now have left that segment of the cervix to which are attached the strong basal portions of the broad ligaments and the uterosacral ligaments. Moreover, these attachments have not been traumatized nor has the normal anatomic relationship of the cervical segment to either the main trunks of the uterine vessels nor to the ureters been disturbed. The anterior and posterior margins of the cervical stump are now approximated by means of a chromic catgut suture introduced exactly in the midline, securely tied and left long for temporary traction purposes. Angle sutures of the same material are next placed on each side which first pass through the posterior margin of the cervical stump then transfix the stump of the round ligament, also that of the uteroovarian ligament if the ovaries are being retained, and finally emerge through the anterior margin of the cervical stump. When tied these sutures snugly appose the round ligaments to the angles of the cervical stump for additional support.

cervical stump and approximated to the canal mucosa by means of interrupted sutures of chromic catgut. The first suture should be introduced in the midline posteriorly and subsequent ones radiating from the canal like the spokes of a wheel until three-fourths of the stump is covered. The anterior one-fourth is later completed. These sutures are left long temporarily, being gathered in the bite of a single clamp as they are tied, and used for traction.

Step 4: Delivery of the Corpus Uteri.—(Figs. 3 and 4.) A retractor is now inserted beneath the bladder, traction downward being maintained upon the cervical stump by means of the sutures thus clearly exposing the vesicouterine peritoneum which is incised transversely. The same caution must be exercised here as is required in opening the peritoneum elsewhere not to cut or traumatize a loop of bowel that



FIG. 5.—The uterine vessels have been divided at the level of the internal os and securely ligated on each side. A subtotal hysterectomy at the level of the internal os is being completed with a deep cupping of the retained cervical stump.

may be presenting just beneath. The subvesical retractor is now shifted into the peritoneal cavity and a quick exploration is made with the fingers to determine the exact status of the uterus and its appendages. Traction downward upon the cervical sutures and upward upon the intraperitoneal retractor exposes the lower segment of the anterior uterine wall through which a traction suture is passed embracing a deep, wide bite. The cervical stump is now pushed back into the posterior vaginal fornix and simultaneously a steady pull is exerted upon the uterine traction suture. This lifts the uterus forward and readily permits insertion of a second traction suture at a higher level in its anterior wall to which the pull is shifted as the first suture is withdrawn. Repetition of this device, which was suggested some years ago by T. S. Cullen, provides a simple and easy method of delivering the corpus uteri into

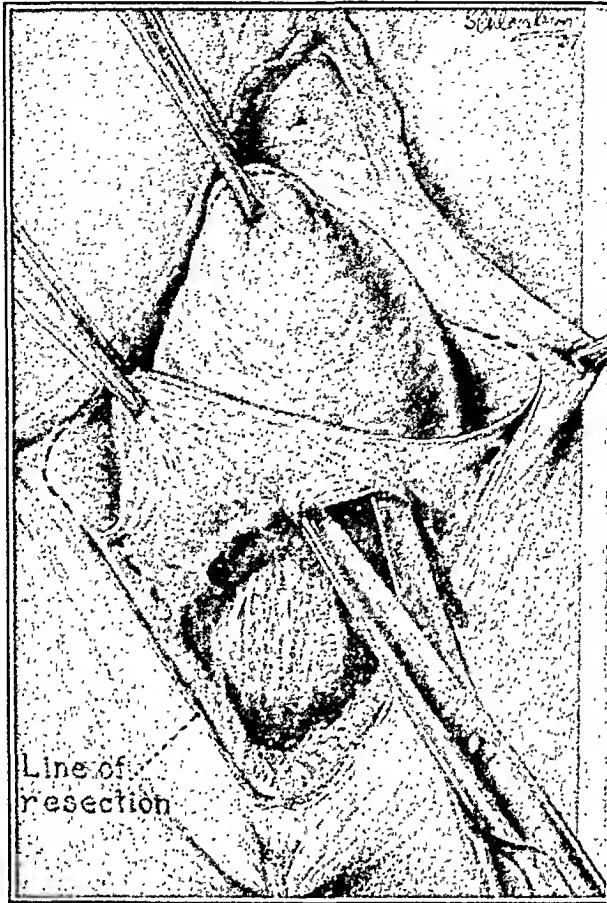


Fig. 9.—The relaxed pelvic floor and large rectocele are here shown. The dotted line indicates the area to be denuded by blunt dissection.

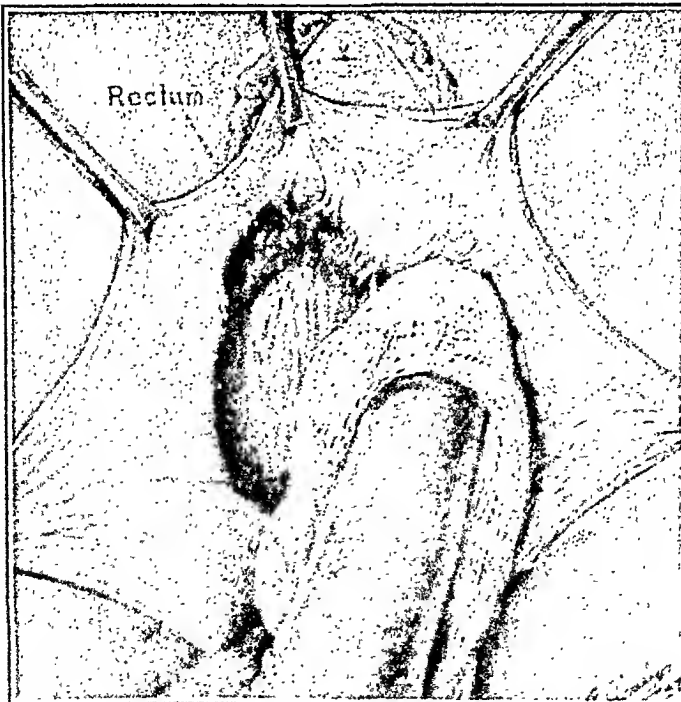


Fig. 10.—Blunt dissection is being used to separate the rectum from the vaginal wall.

Step 7: Transposition of the Cervical Stump.—(Figs. 6 to 8.) At this point we utilize principles borrowed from both the Watkins and the Manchester operations. The two pillars of vesicocervical fascia so carefully isolated and preserved at the beginning of the dissection are now clearly exposed. A stout chromic catgut suture is passed beneath the left one close to its cervical attachment, care being taken to include the entire thickness of this sturdy structure, and is continued as a purse-string along the cut margin of the vesico-uterine peritoneum just beneath the bladder to the midline; here a deep and substantial bite is taken with the needle through the upper margin of the cervical stump, the suture then being further continued toward the right as a purse-string to include the remainder of the peritoneal flap and finally passes beneath the right vesicocervical fascial pillar close to its cervical attachment. When tied this suture, which is quite simple and easy to introduce, closes the peritoneal cavity, anchors the two strong fascial pillars to the cervical stump

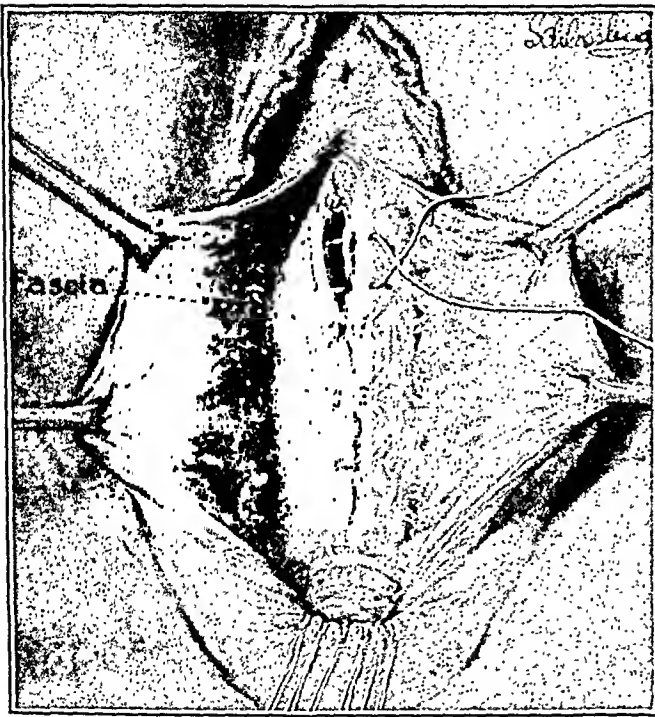


Fig. 7.

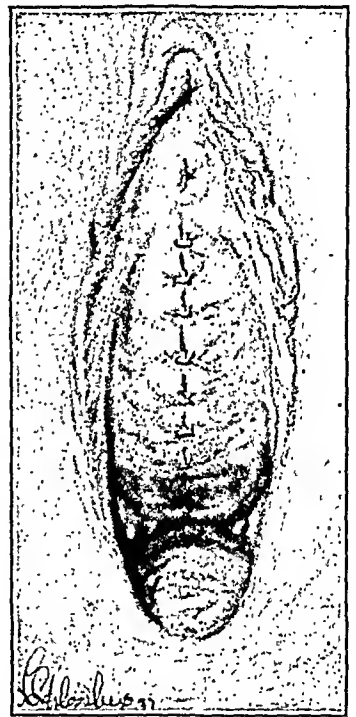


Fig. 8.

Fig. 7.—The bladder has been returned to its normal position and is now strongly supported by both the transposed cervical stump and plication of the stout pubo-cervical fascia.

Fig. 8.—The anterior operation completed.

in a manner similar to the Manchester technique and brings the strongly supported and well-elevated cervical stump snugly up under the bladder just as the uterine corpus is utilized for this purpose in the Watkins operation. Several mattress sutures of chromic catgut are next introduced to imbricate the vesicocervical fascia from the cervical stump forward to within 1 cm. of the urethral meatus. The two flaps of vaginal wall are then pared down to proper size and the anterior wound is neatly closed with interrupted sutures of plain catgut.

Step 8: Reconstruction of the Pelvic Floor and Perineum.—(Figs. 9 to 12.) There remains now only the broken down perineum and pelvic floor together with the commonly associated rectocele to be dealt with. An Allis clamp is applied in the midline posteriorly at the mucocutaneous border, one on each side of the vaginal introitus at the level of the lower border of the hymen and a fourth one at a mid-point of the posterior vaginal wall just above the crest of the rectocele. Simul-

the uterosacral ligaments. The peritoneum of the culdesac is dissected out like a hernia sac, opened, a purse-string suture is introduced about its neck, tied and the sac amputated, after which the uterosacral ligaments are approximated, all according to Ward's technique. The operation is then completed by *Steps 7 and 8*.

COMMENT AND SUMMARY

The admitted incidence of both partial and complete anatomic failure consequent upon utilization of any of the operations commonly employed today in the treatment of advanced grade genital prolapse is undoubtedly responsible for continuation of the search for a more uniformly dependable reconstructive plan, as evidenced by the succession of articles upon this subject to be found in the gynecologic literature of recent years. Inherent defects chargeable to each of the more popular procedures become conspicuously obvious upon a critical comparison of the objective aimed at with that actually attained. Briefly stated, the surgical problem presented by genital prolapse involves: first, complete elimination both of actual and potential disease and, second, restoration with permanent stabilization of normal anatomic relationships. Judged by this standard both colpoeleisis and total colpectomy, while possessing undoubted merit, must be regarded as last resort measures which, even if objectively efficient, are both subjectively and anatomically far from ideal. The entire group of transposition operations are open to the objection that they leave the uterus as a potential source of later benign or malignant disease. In total vaginal hysterectomy the most dependable supporting structures are first partly devitalized by the application of crushing clamps, division and ligation with constricting sutures; these same impaired structures are then relied upon to furnish the central and main support of the entire reconstruction plan.

Now the composite operation here offered avoids the objections to the commonly used procedures noted above. By utilization of the time honored high amputation of the cervix coupled with subtotal vaginal hysterectomy, it eliminates existing and potential uterine disease, thereby also relieving the supporting structures of considerable dead weight; by preserving intact that segment of the cervix to which are normally attached the cardinal and the uterosacral ligaments together with the sturdy pubocervical fascia, ideal conditions are created for adaptation of the most dependable features of the several transposition operations; plication of the vesical sphincter is easily executed; accurate identification and dissection of the pubocervical fascia permits imbrication of this valuable unit beneath the bladder neck and urethra in accordance with the established principles of hernioplasty; suture of the round ligaments into the angles of the cervical stump provides additional lift and support; adequate circulation to the cervical stump and attached structures

taneous traction upon these four clamps clearly defines the triangular area to be denuded of its vaginal mucosa. The simplest procedure is to employ the flap type of dissection with inverted V-shaped resection of the mucosa, extending the apex well above the upper margin of the rectocele. Completion of the denudation exposes the anterior rectal wall, which is freely separated by blunt dissection from the adjacent posterior vaginal wall and pushed back into place. The levator ani muscles together with their overlying fascia are now approximated as one layer by means of three interrupted, buried chromic catgut sutures each one of which is introduced 1 cm. mesial to the skin margin and includes a bite of at least 1.5 cm. in breadth and depth of the fascia and its underlying muscle. The upper one of these sutures is passed as a crown suture according to Emmet's technique. When tied

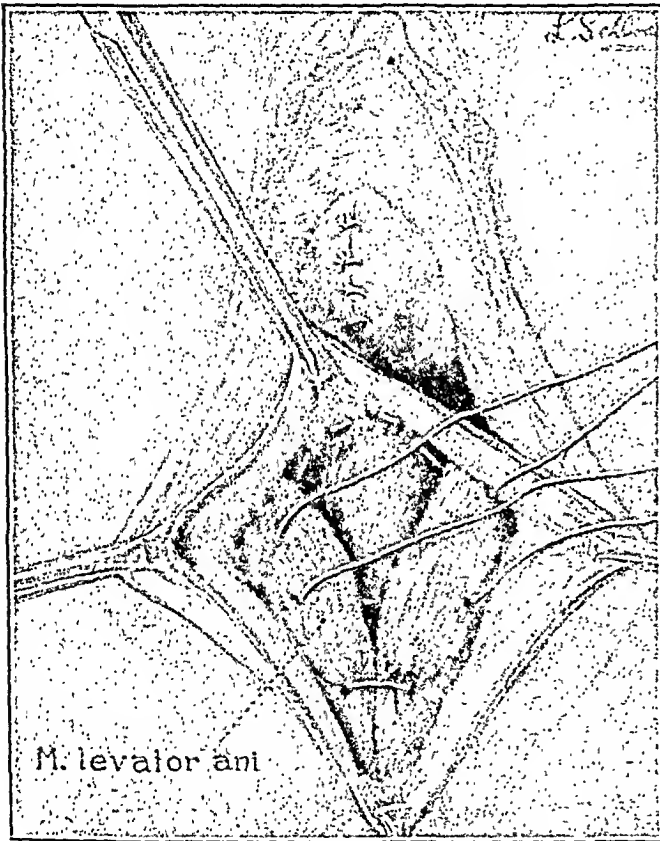


Fig. 11.

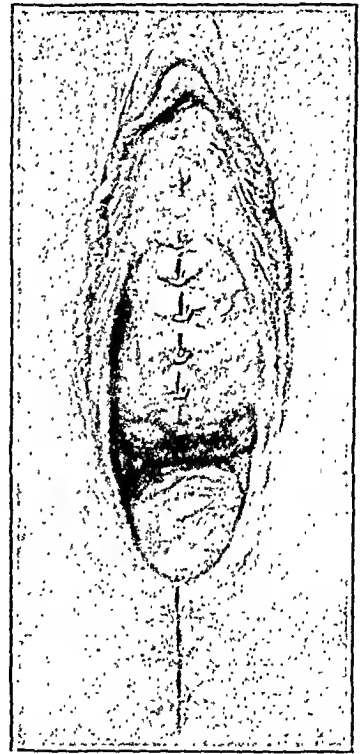


Fig. 12.

Fig. 11.—The levator ani muscles together with their overlying fascia are being approximated as one layer over the rectocele by interrupted sutures of chromic catgut. The redundant flap of vaginal wall has been pared down to proper size.

Fig. 12.—The operation completed with reconstruction of a vagina of normal caliber and depth and restoration of normal anatomical relationships having been achieved.

these sutures reconstruct the pelvic floor, flatten out the posterior vaginal wall, cure the rectocele and narrow the vaginal orifice to any desired extent. The more superficial zone of fascia purposely left between these three sutures and the skin margin when they were introduced is now approximated over them by a continuous suture of plain catgut and the surface wound is closed with a subcutaneous suture of the same material.

If in addition to the rectocele one is confronted also with an enterocele, it is necessary to complete the posterior dissection prior to Step 7. An index finger inserted over the cervical stump into the bottom of the culdesac guides the operator in continuing the separation of the rectum from the posterior vaginal wall quite up to

A comparable number of operations having been performed since the last series was analyzed (221) it seemed desirable to review the results obtained in both series. This was especially indicated in the light of the more than complete substitution of the interposition operation by vaginal hysterectomy as the operation of first choice.

Coventry and Moe³ compared the end-results in a similar series of 100 patients. Seventy of the 76 patients on whom the interposition operation was performed were followed and 69 (98.6 per cent) showed successful end-results, there being only one failure. On the other hand, there were 34 treated by vaginal hysterectomy. Twenty-five of the thirty which were followed in this group were successful, five or 16.7 per cent ending in failure.

This series deals with 221 consecutive operations for the relief of prolapse of the uterus as against 220 operations in the previous series. The group of operators remains essentially unchanged. In this series the ages of the patients ranged from twenty-two to seventy-five with an average of 46.2 years. This average is practically identical with our previous series and with the figures given in the literature.

TABLE I. AGE INCIDENCE

		1928 SERIES	1937 SERIES
Youngest 22	Oldest 75	Average 45.8	46.2
Under 30		12	12
30-40		55	60
40-50		80	63
50-60		26	46
60-70		33	33
70 and over		6	7

The women in this series bore a total of 815 children, an average parity of 3.8. The total number and range of parity compares very closely with the previous series.

TABLE II. PARITY INCIDENCE

	1928 SERIES	1937 SERIES		1928 SERIES	1937 SERIES
Nulliparas	5	4	Para viii	9	6
Primiparas	16	18	Para ix	4	7
Para ii	39	48	Para x	5	3
Para iii	44	37	Para xi	2	
Para iv	29	43	Para xii	3	
Para v	25	22	Para xiii	1	
Para vi	21	15	Para xiv	1	1
Para vii	8	9	Average parity	4.2	3.8

Sterilization was done 33 times (14.9 per cent). The disparity in the frequency of this operation in this series with the previous series 102 times (46.8 per cent) is obviously due to the replacement of the interposition operation by vaginal hysterectomy.

is assured through preservation of the adjacent main trunks of the uterine vessels and their branches; the ureters are not endangered by any step of the operation; obliteration of the culdesac and plication of the uterosacral ligaments for associated enterocele are readily effected; and, finally, reinforcement of the rectovaginal fascia together with reconstruction of the pelvic floor and perineum completes the operation with accurate restoration of normal anatomical relationships having been achieved. Attention is again called to the fact that every important step of the operation is borrowed from an already well established procedure in the treatment of vaginal herniae. Immediate results in the small series of cases thus far dealt with by this method, totaling about twenty-five, have been completely satisfactory.

9 EAST CHASE STREET

PROLAPSE OF THE UTERUS—SHIFTING TRENDS IN TREATMENT*

JOSEPH L. BAER, M.D., RALPH A. REIS, M.D., AND
ROBERT M. LAEMLE, M.D., CHICAGO, ILL.

(From the Department of Gynecology and Obstetrics, Michael Reese Hospital)

AN ANALYSIS of 220 operations for prolapse of the uterus and the end-results obtained by the various operations employed was published in 1928.¹ These operations were performed by the Gynecological Staff of the Michael Reese Hospital and include a number of procedures.

The procedure most frequently employed, the interposition operation, was done in 41 per cent of the series since for many years this operation, when indicated, had proved eminently satisfactory. In the literature current ten years ago vaginal hysterectomy was being advanced as the ideal operative procedure for the average instance of prolapse in women past the child bearing age.² With this in mind vaginal hysterectomy spontaneously displaced the interposition operation as the procedure of choice of the Gynecological Staff of the Michael Reese Hospital.

As we stated in the previous communication, the gynecologist, confronted with the problem of curing a patient afflicted with prolapse of the uterus is influenced by three factors in his choice of operation; first, by the limitations and conditions in the given patient; second, by his familiarity and previous success with particular types of operations; and third, by his desire to improve his results through the utilization of other methods.

*Read at the Sixty-Second Annual Meeting of the American Gynecological Society, Swampscott, Mass., May 31 to June 2, 1937.

uteri through the vulva. The objections to this classification are based on the fact that the term "complete prolapse of the uterus" should apply only to those instances in which the entire organ is found beyond the introitus. The classification, however, labels both this condition and protrusion of only the cervix as third-degree prolapse. If the term "procidencia" were reserved for complete prolapse as defined above then the current classification would not be contradictory. We are of the opinion that this classification amplified by the correct use of the term *procidencia* justifies itself on an anatomic pathologic basis.

It will be noted in Tables I to V given above that enterocele was diagnosed only three times (1.4 per cent) in the series of 1928. In the present series this condition was recognized seven times (3.1 per cent) preoperatively and was discovered subsequent to operation in two additional patients, a total incidence of nine (4.1 per cent). Among the seven patients in whom it was recognized there was one failure following vaginal hysterectomy and repair of the enterocele. This comment was made in the previous article, "If the deep Douglas is a predisposing factor in the development of prolapse of the uterus, the number noted here would seem too small. Either many instances of deep Douglas were overlooked or its significance has been overestimated."

The frequency of this congenital defect, which is regarded as a predisposing factor in the occurrence of enterocele and in the failure of operative cure or prolapse of the uterus has not been accurately determined. Enterocele occurred only nine times (4.1 per cent) in this series.

Previous Operations.—Twenty women in this series of 221 had been operated upon 24 times previously for the cure of their prolapse, one having been operated three times and two twice each. Table VI shows the operations selected in the presence of failure, both in this series and in the series of 1928. It will be noted that vaginal hysterectomy was selected ten times as the method of choice in the presence of a previous failure, whereas in the previous series the interposition operation occupied the leading position. Evidently the operators were definitely in earnest in their determination to evaluate vaginal hysterectomy as a cure for prolapse of the uterus.

TABLE VI

	SERIES 1928	SERIES 1937
Interposition	9	2
Le Fort	6	6
Ries fixation	5	
Ventrofixation	5	
Extrascial fixation	4	
Ventrosuspension	1	
Vaginal hysterectomy	1	10
Supravaginal hysterectomy		
With stump fixation	1	1
Vaginal plastic		1
Panhysterectomy		1

TABLE III. STERILIZATION

	1928 SERIES	1937 SERIES
Sterilized	46.0%	14.9%
Sterilized previously	1.3%	
Postmenopausal	40.0%	41.1%

Analysis of Symptoms.—This group showed a considerable increase in two of the outstanding symptoms as compared with the previous series; namely, protrusion and bladder distress.

TABLE IV. SYMPTOMS

	PERCENTAGES IN	
	1928 SERIES	1937 SERIES
Protrusion	58.6	83.7
Discomfort	53.6	46.1
Abdominal pain	18.1	8.1
Backache	28.1	23.1
Bearing down	17.3	14.9
Bladder distress	33.6	40.6
Frequency	30.0	20.8
Dysuria	13.1	10.4
Incontinence	5.4	9.4
Leucorrhea	8.6	14.4
Dysmenorrhea	5.3	1.3
Menorrhagia	7.6	8.5
Metrorrhagia	4.5	9.5

Pathology.—The classification of prolapse commonly accepted and adhered to in the previous publication remains the generally accepted one. First-degree prolapse is defined as a descent of the uterus in which the cervix reaches the level of the ischial spines; second-degree prolapse is a descent of the uterus in which the cervix appears at the vulva; and third-degree prolapse is a protrusion of the cervix or corpus

TABLE V. PATHOLOGY

	PERCENTAGE IN	
	1928 SERIES	1937 SERIES
Prolapse		
First degree	11.4	7.8
Second degree	33.2	35.2
Third degree	55.4	57.0
Cystocele and rectocele	73.6	73.7
Rectocele only	9.5	11.8
Enterocele	1.4	3.1
Fibroids	9.0	17.7
Fibrosis uteri	2.7	2.4
Adenomyosis		5.9
Diseased cervix	24.5	30.7
Polyp	1.3	7.2
	Cases	Cases
Ovarian cyst	5	11
Ovarian fibroid	1	1
Pregnancy		2
Diabetes	6	4
Cardiovascular renal	6	7
Salpingitis	1	1

renal disease and coronary sclerosis. The operation was done under local infiltration anesthesia. The patient promptly developed bronchopneumonia and succumbed after twelve days. An ulcerated necrotic adenocarcinoma of the corpus uteri was found at autopsy. There had been no preliminary curettage at the time of operation. The second death occurred in a sixty-six-year-old para ix. This patient was operated upon under ethylene and died suddenly on the sixth day of pulmonary embolism. In the remaining 27 patients there was no morbidity except in one patient who had fever for one day (morbidity 3.7 per cent). Five patients (18.5 per cent) required catheterization and the average hospital stay was 14.4 days.

Ventrosuspension and Vaginal Plastic.—Thirteen patients were operated upon by the Gilliam method of ventrosuspension. A vaginal reconstruction was done in each instance. There was no mortality and the gross morbidity was 7.7 per cent. This is represented by one patient who had a secondary hemorrhage from the plastic operative site. Three patients (23.0 per cent) required catheterization. The average hospital stay was 13.4 days.

Manchester Operation.—There were nine patients operated upon by various modifications of the Manchester procedure⁵ with a gross morbidity of 33.3 per cent, which included one instance of sepsis, one instance of pelvic peritonitis, and one of cystopyelitis. Three patients (33.3 per cent) required catheterization and the average hospital stay was 14.8 days.

Vesicofixation.—The Halban-Porges vesicofixation operation⁶ was done six times. There were no deaths. Morbidity occurred in three patients (50 per cent) which included one urinary tract infection and two instances of fever. Three patients (50 per cent) required catheterization and the average hospital stay was 16.8 days.

Extrascapular Fixation.—The Koehler extrascapular abdominal fixation⁷ was done four times. There were no deaths. There was a morbidity of 25 per cent due to one wound infection. Catheterization was necessary in one patient (25 per cent). The average hospital stay was 15.2 days.

Ventrofixation and Vaginal Plastic.—Eight patients were operated upon by ventrofixation of the uterus and vaginal plastic. There was no mortality and the gross morbidity was 12.5 per cent due to the development of sepsis, peritonitis, and a jejunal fistula in one patient. Following recovery from the infection, this fistula was repaired with good results. Two patients (25 per cent) required catheterization and the average hospital stay was 24.1 days.

Supravaginal Hysterectomy.—Three patients were treated by supravaginal hysterectomy and vaginal plastic. There were no deaths. Morbidity included one patient who had fever for several days, one patient required catheterization and the average hospital stay was fifteen days.

Operative Procedures.—Table VII shows the frequency with which the various operative procedures were employed in the present series.

TABLE VII. OPERATIVE PROCEDURES

	1928 SERIES	1937 SERIES
Mayo vaginal hysterectomy	7	116
Watkins interposition	91	30
Le Fort vaginal oclusions	14	29
Ventrosuspensions and plastic	14	13
Manchester		9
Ventrofixations and plastic	27	8
Halban-Porges		6
Koehler extrafascial fixations	13	4
Supravaginal hysterectomy and plastic	5	3
Panhysterectomy and Plastic		3
Cervical stump fixations	2	
Kielland-Wertheim interposition	2	
Ries abdominal fixations	28	
Vaginal plasties	17	

Mouth temperatures of 101° F. were considered morbidity in calculating gross morbidity. The value of figures on corrected morbidity is debatable at best. In this paper no attempt has been made to develop figures on corrected morbidity and the comparison with the previous series is shown only in terms of gross morbidity.

Vaginal Hysterectomy.—There were 116 (52.5 per cent) vaginal hysterectomies with one death (0.86 per cent). This occurred in a sixty-three-year-old para v, known to have cardiovascular renal disease with marked hypertension. A vaginal hysterectomy and vaginal occlusion were done under spinal anesthesia. Death occurred on the fifth day due to a postoperative lobar pneumonia. The gross morbidity was 50 per cent. There were fifteen instances of infection of the urinary tract, 5 secondary hemorrhages, and 11 postoperative infections, ranging from stump exudates to two instances of sepsis and one of pelvic peritonitis. Further, there was a postoperative pneumonia, one lung collapse, one bilateral peritonitis and one thrombophlebitis. The remainder (23) was the group of patients with fever and no localization. Sixty-two patients (53.5 per cent) required catheterization more than once. The average hospital stay was 15.3 days.

Interposition Operation.—There were 30 (13.6 per cent) interposition operations. There were no deaths and the gross morbidity was 40 per cent. This included three urinary tract infections, one postoperative hemorrhage, one thrombophlebitis, and one pneumonia. The remainder (six patients) had fever without localization. Thirteen patients (43.3 per cent) required catheterization and the average hospital stay was 13.7 days.

Vaginal Occlusion.—The Le Fort vaginal occlusion operation⁴ was done 29 times. There were two deaths in this group. One death was in a seventy-two-year-old, para vi with a known marked cardiovascular

these 46 (70.7 per cent) presented successful end-results. Twelve (18.4 per cent) were partially successful. Seven (10.8 per cent) had a prolapse of the vagina and were classified as failures.

Interposition Operation.—In 19 patients in whom the interposition operation was done, the outcome was completely successful in 17 (89.5 per cent); there were two partial successes (10.5 per cent) and no failures.

Le Fort Vaginal Occlusion Operation.—End-results were obtained in 18 women. Of these, 17 (94.4 per cent) were successful and there was one (5.6 per cent) failure.

TABLE IX. FOLLOW-UP RESULTS

OPERATION	NO. FOL- LOWED	1928 SERIES			NO. FOL- LOWED	1937 SERIES		
		SUC- CESS	PARTIAL	FAIL- URE		SUC- CESS	PARTIAL	FAIL- URE
Entire series	121	85.8	6.1	8.1	127	78.7	14.2	7.1
Interposition	64	87.5	4.7	7.8	19	89.2	10.8	
Vaginal hyster- ectomy	5	100.0			65	70.7	18.4	10.9
Vaginal occlusion	10	100.0			18	94.4		5.6
Ventrosuspension	11	91.0		9.0	6	66.6	33.4	
Ventrofixation	19	94.7		5.3	4	75.0	25.0	
Kocher	12	100.0			4	75.0		25.0

CHOICE OF OPERATION

The interposition operation was completely successful in 56 out of 64 (87.5 per cent) in the series previously published. In the present series, the interposition operation was successful in 17 out of 19 (89.5 per cent). Vaginal hysterectomy, to which we turned in order to improve our results and the results of which were followed in 65 women, was successful in only 46 instances (70.7 per cent). The patients in both series were operated upon by the same group of gynecologists. Since it may be assumed that these operators were equally competent in both types of operation, the results obtained emphasize the superiority of the interposition operation over vaginal hysterectomy in our hands.

In the light of this outcome it seems appropriate to quote from the 1928 report as follows:

“The value of the Mayo vaginal hysterectomy for the cure of prolapse of the uterus cannot be discussed further than to point out that preservation of the uterus and its utilization has seemed fundamental to the gynecological department of the Michael Reese Hospital. The results presented here apparently justify a continuation of those types of operation in use at present.”

It is our intention to again avail ourselves of the interposition operation as a cure for prolapse of the uterus wherever the conditions for its selection are met. To quote from the previous report “it is selected for those patients with a large cystocele, a corpus uteri neither too large

Panhysterectomy.—Three patients were treated by panhysterectomy. There were no deaths. All three patients had fever (100 per cent), one of these developing a vesicovaginal fistula and one a wound infection. One patient required catheterization and the average hospital stay was 31.3 days.

TABLE VIII. OPERATIVE RESULTS

OPERATIONS	1928 SERIES			1937 SERIES		
	NO.	DEATHS	GROSS MORBIDITY PER CENT	NO.	DEATHS	GROSS MORBIDITY PER CENT
Interposition	91	1	55.1	30		40.0
Vaginal hysterectomy	7	1	43.0	116	1	50.0
Ries fixation	28	1	35.7			
Ventrofixation and plastic	27		44.4	8		12.5
Vaginal plastic	17		11.8	9		33.3
Vaginal occlusion	14		21.7	29	2	3.7
Ventrosuspension	14		57.1	13		7.5
Extrafascial fixation	13		46.0	4		25.0
Supravaginal hysterectomy and plastic	5		60.0	3		33.3
Cervical stump fixation	2					
Panhysterectomy and plastic				3		100.0
Kielland-Wertheim interposition	2	1				
Halban-Porges				6		50.0
Total and average	220	4 (1.8%)	44.5	221	3 (1.3%)	37.7

REMOTE RESULTS

The end-results in this series were determined by examination made either by the operator or by some other member of the department, as in the previous series. The obtainable records of those women who were reexamined from four months to seven years postoperative supply the data for the analysis of remote results. Criticism of conclusions as to remote results in less than two years after operation is justifiable. Still it is undoubtedly true that the vast majority of failures is seen promptly after operation. Since the same period of observation was used in the previous series, it was again utilized here to afford us a basis of comparison.

There were three deaths among the 221 patients (1.3 per cent). Remote results were obtained in 127 patients (57.4 per cent). One hundred (78.7 per cent) were successful, 18 (14.2 per cent) were partially successful, and 9 (7.0 per cent) were failures. The operative end-result, as with the previous series, was considered only partially successful, if a third-degree prolapse recurred as a first-degree prolapse or if a cystocele or rectocele recurred. Combining the improved and cured groups, 118 (92.9 per cent) were successful.

Vaginal Hysterectomy.—This operation practically replaced the interposition operation. Sixty-five patients were followed, and among

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104 SOUTH MICHIGAN AVENUE

DISCUSSION ON PAPERS BY DR. JOSEPH L. BAER AND DR. EDWARD H. RICHARDSON

DR. THOMAS C. PEIGHTAL, New York, N. Y. (By Invitation).—Our attack upon the problem of prolapse has received new impetus in recent years from a better anatomic knowledge of the true supporting structures of the uterus and vagina. This knowledge has served as a stimulus to devise new operative procedures, but, for the most part, it has been responsible for reviving and popularizing certain older principles of technic not commonly used in the average clinic. For the same reason on many services there is at present a desire to appraise the end-results of previous methods and to re-plan an operative attack based upon both past experience and this newer knowledge.

The two papers under discussion do exactly this. Dr. Richardson, having found figures which favor the interposition operation over total vaginal hysterectomy, has used this experience in devising a composite operative procedure which is carefully designed to meet all the complex problems of extensive uterine prolapse and vaginal hernias in elderly women. The interposition principle is emphasized, the parametrial fixation feature is introduced, and the value of removing the pathologic portions of the uterus when indicated, is not lost. Cystocele, rectocele, enterocele, and relaxed urethral sphincter also are corrected. The retention of at least an outer cuff of the upper portion of the cervix provides the keystone, so to speak, upon which the interposition and parametrial fixation principles of this procedure are built. Some may level criticism at the retention of this portion of the cervix, but, as Dr. Richardson uses it, there is no doubt that he not only avoids devitalization of its ligaments but that he secures a firmer attachment of them. The other features of the operation are all well proved principles upon which there can be no controversy.

In Dr. Baer's paper the chief interest lies in his estimate of the comparative effectiveness of the Watkins interposition operation and the Mayo vaginal hysterectomy. The fact that these two series have come from the same group of operators has eliminated many of the variable factors which confuse the usual statistical studies.

In order to formulate better our own conclusions concerning remote results in the operative treatment of prolapse, we have analyzed briefly 111 followed cases over the five-year period up to January 1, 1936, at the Roosevelt Hospital. Of this group, one-fifth had complete prolapse (procidentia) while four-fifths had varying degrees of partial prolapse. In the procidentia group interposition operation was done twice as often as vaginal hysterectomy, but vaginal hysterectomy gave more successful results. In the partial prolapse group there were mainly three operations: one-half were treated by a vaginal plastic combined with ventrosuspension or fixation; one-third by the interposition operation, because of the degree of the cystocele; and one-sixth by vaginal hysterectomy, mainly because of the amount of the descensus. In this partial prolapse group, the interposition operation was just as superior to the other procedures as Dr. Baer has indicated in his paper. Late

nor too small, freely movable and without gross adnexal pathology."

Vaginal hysterectomy will be restricted to those instances of prolapse in which the pathology of the uterus itself carries the indication for hysterectomy. The Le Fort vaginal occlusion operation should retain its value for older women with atrophy of the cervix and with senile atony of the anterior and posterior fascial and muscular structures and in whom marital relations have terminated.

In women with prolapse in whom childbearing is to be conserved, we have heretofore recommended ventrosuspension combined with a vaginal reconstruction. We still maintain this position in regard to third-degree prolapse. Both the Manchester operation and the Halban-Porges vesicofixation are superior in first and second-degree prolapse. We have not determined to our satisfaction which of these various methods is best suited for the cure of prolapse plus conservation of childbearing.

SUMMARY

In 221 operations for prolapse of the uterus, the average age was 46.2 years and the average parity was 3.8. Ninety-one patients (41.1 per cent) were in the menopause and 33 patients (14.9 per cent) were sterilized. Seventeen patients (7.8 per cent) had a first-degree prolapse, 76 (35.2 per cent) had a second-degree prolapse, and 123 (57 per cent) had a third-degree prolapse. Ten types of operations were employed. Based on the immediate and remote results, three of these are well suited to meet particular indications; namely, the Watkins interposition operation, the Le Fort vaginal occlusion operation, and the Mayo vaginal hysterectomy. We believe the interposition operation should take precedence over vaginal hysterectomy wherever the conditions for its selection are met. Vaginal hysterectomy should be restricted to prolapse in which the pathology of the uterus itself carries the indication for hysterectomy.

The Le Fort vaginal occlusion operation is indicated for older women with atrophic genitalia in whom marital relations have terminated. For the childbearing group the choice lies between the Manchester operation and the Halban-Porges operation for first- and second-degree prolapse. The Gilliam suspension operation, combined with vaginal reconstruction is best suited for third degree prolapse.

There were three deaths (1.3 per cent). One was from lobar pneumonia, one from bronchopneumonia, and one from pulmonary embolism.

End-results by personal examination were obtained after 127 operations (57.4 per cent). Of these 100 (78.7 per cent) were successful, 18 (14.2 per cent) were partially successful, and 9 (7.1 per cent) were failures. Combining the cured and improved groups, 118 (92.9 per cent) were successful.

Acknowledgment is hereby made to the members of the Gynecological Staff of the Michael Reese Hospital for the use of their records.

accord with this statement, and believe it is the whole gist of the matter. The judgment of the surgeon in selecting the type of operation for each case determines the ultimate result.

In cases where it is advisable to conserve the uterus, I believe that the cure of prolapse should be accomplished by utilizing the principal support of this organ, namely the cardinal ligaments, reefing them by approximation in front of the cervix, or shortening them by the interposition operation.

We hear much about the Manchester operation today. It is correct in principle because it utilizes the normal supports of the uterus. Donald used this technic in 1888, but it was not until Fothergill perfected and published the operation in 1907 that it became popular. In his paper he gives credit to Alexandroff in 1903 and Tweedy of Dublin in 1905 for publishing their technic and stressing the importance of using the paraervical tissues to give the necessary support.

These slides I show, which were taken from the original illustrations, prove that great minds have thought in the same channels for many years past. Emmet in 1869 utilized the same principle. He denuded the vaginal fornix on each side of the cervix at the base of the broad ligament and an area anterior to the cervix. He brought these three points together with silver wire, thus approximating the base of the broad ligaments in front of the cervix. In 1912 Baldwin of Brooklyn improved this technic and reported excellent results. Alexandroff in 1903 placed a suture in each cardinal ligament and crossed them, and then sutured the ligaments together in front of the cervix. Again we see the same principle employed by Tweedy in 1895. E. C. Dudley of Chicago in 1906 published his operation where he cut the cardinal ligaments from the cervix and sutured them together and to the front of the cervix. Hertzler of Kansas in 1906 published the same technic but overlapped the ligaments. He stated he had been doing it with success for four years. Nyulasy of Australia in 1908 accomplished the same result but from above. Halban's technic in 1919 has the same principle.

In the nonchildbearing age, where there is uterine pathology present, the Mayo type of operation gives excellent results, provided an enterocele is eliminated or prevented by dissecting out the peritoneal pouch of Douglas and uniting the uterosacral ligaments. In 116 cases of this type I found 83 per cent had some pathologic condition of the uterus which made removal of the organ desirable.

DR. HERMAN J. BOLDT, WHITE PLAINS, N. Y.—Where sexual relations have ceased, in elderly women, and where there is complete procidentia of the uterus and vagina, I have not found any form of operation that will equal the complete extirpation of both uterus and vagina. This is an operation that was devised many years ago by Dr. Edebohls. I have done it whenever it was indicated. It is done much more rapidly than any other operation; there is no more morbidity and it brings an absolutely perfect cure.

DR. LILLIAN K. P. FARRAR, NEW YORK, N. Y.—There is one point in technic I would like to mention. When in performing a vaginal hysterectomy for prolapse of the uterus and either the broad ligaments or the cervix are fastened forward, the intraabdominal pressure will then fall on the stretched-out uterosacral ligaments and an enterocele is almost sure to develop. It is a simple matter to unite the uterosacral ligaments and prevent this occurrence. I believe that utilizing the cervix as Dr. Richardson has described is a valuable procedure.

Several years ago Dr. Howard A. Kelly brought to me a patient who had had a supravaginal hysterectomy done twenty years before, and who then had a prolapse of the cervix and a large cystocele. I decided to split the cervix and dissect off the mucous membrane and vaginal mucosa, suture the stump to the pubis and sew the fascia below as in a Watkins operation. The result was absolutely satisfactory,

results of the total group, graded after the manner used by Dr. Baer, show figures almost identical to his, 77 per cent successful, 16 per cent partially successful, and 7 per cent failures.

Over the five years the incidence of the various operations used indicates a definite trend. In procidentia, there is a tendency to use vaginal hysterectomy more often and interposition less often. In partial prolapse the trend is to use plastic repair plus ventrosuspension if the cystocele is of moderate degree, interposition operation if the cystocele is large and with not too much uterine descensus, while vaginal hysterectomy is reserved for those cases where descensus is the main factor. Ventrofixation, formerly practiced, has not been done in three years.

DR. WALTER T. DANNREUTHER, NEW YORK, N. Y.—Vaginal hysterectomy, interposition of the uterus, and the Manchester operation are probably the most popular reconstructive methods at the present time, and I believe that most of us have been satisfied with the end-results. Bullard has reported 95 per cent cures after vaginal plastic surgery in 461 cases done by 30 different operators, which is not far from Dr. Baer's report of 92.2 per cent successes. The 4 per cent incidence of failure after the interposition operation, reported by Dr. Richardson, is not at all high, but 30 per cent of failures after vaginal hysterectomy is not only discouraging but astonishing.

Dr. Baer's presentation indicates that the trend at the Michael Reese Hospital is now back toward the interposition operation. This is apparently due to the fact that vaginal hysterectomy has been followed by an incidence of 10.8 per cent failures, contrasted with none after the interposition operation. This discrepancy would be more significant if the statistics represented the work of a single operator.

It is difficult to agree with Dr. Baer's assumption that all of "these operators were equally competent in both types of operation." Even if this were true, there would still be variation in the selection of cases, differences in surgical judgment, and modifications of technical details, all of which have a direct influence on the end-results. It would be interesting to know how closely Dr. Baer's personal results correspond with the figures furnished by the group of operators.

The interposition operation is absolutely contraindicated before the menopause. Pregnancy, fibroids, and carcinoma in a transposed uterus are serious therapeutic problems. A diagnostic curettage should precede an interposition operation without exception.

DR. JAMES C. MASSON, ROCHESTER, MINN.—There is a legitimate field for both the Mayo type of vaginal hysterectomy and the Watkins-Wertheim interposition operation. The interposition operation gives the best results in cases in which there is a marked cystocele but a prolapse of not more than the second degree. On the other hand, a vaginal hysterectomy is indicated in patients with large cystocele and also marked prolapse of the uterus.

To extend the field of usefulness of the interposition operation, I frequently reduce the size of the uterus in women close to the menopause age by excising the greater part of the anterior wall, all the endometrium, and all the cervix. It is a rather bloody operation, but I feel that it is preferable to doing a subtotal hysterectomy and leaving the cervix, which is more likely to give trouble than any other part of the uterus. By this operation we effectively sterilize the patient, reduce the danger of any tumors developing in the uterus and in a large measure protect against leucorrhea.

DR. GEORGE GRAY WARD, NEW YORK, N. Y.—Dr. Richardson stresses the complexity of the surgical problem and states that there is not a single plan of reconstructive surgery yet devised that is applicable to all types. I am heartily in

AN UNUSUAL OBSTETRIC INJURY CAUSING DETACHMENT OF BLADDER AND URETHRA FROM THE SYMPHYSIS PUBIS AND COMPLETE EPISPADIAS*

GUY L. HUNNER, M.D., BALTIMORE, Md.

(From the Gynecological Service of the Johns Hopkins Hospital)

THE following case report seems worthy of publication because of the unusual character and extent of the obstetric injury, and because of the problems encountered in attempting to restore the patient's control of her bladder function.

Mrs. B. M., aged thirty-eight years, at term with her first pregnancy, entered the Church Home and Infirmary on Aug. 28, 1935. The fetal head was engaged in the L.O.A. position and labor progressed very slowly with alternate recessions until, at the end of sixty-six hours, the cervix seemed fully dilated and the membranes ruptured. The second stage took one hour and twenty minutes and ended with the precipitate expulsion of a normal male child weighing 8 pounds and 5 ounces. It was apparent that the patient had received extensive lacerations and Dr. Gerald Ackerman, the assistant resident surgeon, was called and on his arrival the third stage of labor had ended normally. The patient was placed under light general anesthesia.

Examination revealed an inverted T laceration extending from the clitoris downward, exposing the deep fascia over the lower portion of the symphysis pubis. The tissues of the vestibule had been swept away. The external urethra at first could not be located. The laceration extended to the anterior cervix where it branched laterally to form the inverted T, suggesting the preliminary incision for an interposition operation. Both triangular flaps of the anterior vaginal wall had been denuded from the underlying tissues of the base and posterior walls of the bladder, and these bladder walls now protruded as a large cystocele. On further search for the urethra, pressure over the cystocele caused a free gush of urine from an opening situated several centimeters back of the symphysis pubis. It was then found that the entire anterior wall of the bladder together with the urethra had been torn from their attachments in the symphysis region. The anterior wall of the urethra had been laid wide open (Fig. 1), and the tear had extended through the muscles of the internal sphincter and for a short distance up the anterior wall of the bladder.

In his repair work Dr. Ackerman placed a mushroom catheter in the bladder and, using interrupted sutures of twenty-day chromic catgut, began at the upper end and brought together in succession the torn edges of the bladder, the internal sphincter region, and the anterior wall of the urethra. He then attempted with the same suture material to get anchorage in the periosteum of the region of the pubic arch and draw the prolapsed tissues forward beneath the symphysis. Finally, the posterior walls of the bladder forming the cystocele were covered with the denuded vaginal flaps by interrupted sutures which completed the approximation of the inverted T laceration.

*Read at the Sixty-second Annual Meeting of the American Gynecological Society, at Swampscott, Mass., May 31 to June 2, 1937.

and I have followed this procedure in similar cases since, so I am glad to endorse heartily the technic Dr. Richardson has presented.

DR. WILLIAM C. DANFORTH, EVANSTON, ILL.—Two hundred and three vaginal hysterectomies have been carried out in the past few years on our service. Eighty were done for a descensus of greater or less degree. In this group we had three distinctly poor results, and two or three others which were unsatisfactory. These poor results are due particularly to failure to adopt a precaution which Dr. Farrar has mentioned, that is, the suturing of the uterosacral ligaments.

DR. BAER (closing).—Dr. Peightal drew exactly the right conclusion, that we are limiting the place of vaginal hysterectomy and shifting back to the interposition operation. We are now much interested in the Manchester operation. The operation has, however, a limited place in women of the childbearing age, with complete prolapse. We believe the Gilliam ventrosuspension is the procedure of choice for complete prolapse, and the Manchester is better for partial prolapse.

Dr. Dannreuther's comment was entirely pertinent. The single series results perhaps lend themselves better to conclusions than group series, and yet we believe that the group in which I work is a fairly well-coordinated group and so we feel justified in presenting a summation of our results and a comparison of the two series. My personal results closely parallel those of the group.

Of course, pregnancy, carcinoma, and fibroids may develop in the interposed uterus. The incidence is fortunately very, very low. And if the interposition operation has the merit which most of you seem to believe it has when properly selected, I still think it should be chosen plus sterilization even in the menstruating woman, regardless of the possibility of the three types of pathology developing in such an interposed uterus.

The technic of the interposition operation must be properly carried out, as in all others; the patient must be well selected, and the result then is satisfactory. I am particularly glad that the Society accepted this rebirth of the interposition operation, because I think it was being slowly shelved, and I am glad to have had some small part in recalling it to your attention.

The mutilation of the uterus which Dr. Masson indicated is desirable in some instances of interposition, but this procedure which he himself characterized as a bloody operation, might perhaps be replaced by what Dr. Richardson suggests in his paper, the modified interposition plus the Manchester characteristics.

repair work had given way except possibly in the anterior wall of the bladder where healing had taken place down to but not including the internal sphincter.

The tissues of the anterior wall of the bladder and of the urethral region had again prolapsed backward away from the symphysis region, and the anterior wall of the urethra including the internal sphincter region lay wide open.

Immediately beneath the symphysis there was a diamond-shaped opening measuring about 2 cm. on each of its 4 sides. Its anterior legs met at the symphysis joint and were composed of the inferior edges of the pubic rami denuded of all tissues down to the periosteum. The posterior borders of the diamond-shaped opening met at the external orifice of the urethra and were composed of the widely gaping tissues about the external orifice, and by the prolapsed tissues of the vestibule region of the anterior vaginal wall, which probably contained torn fragments of the ischio-cavernosus, bulbocavernosus and deep transversus perinei muscles. The antero-posterior measurement of the diamond-shaped opening from the symphysis to the external urethra was about 2.5 cm. With reflected light from the head mirror one could look through this opening into the space of Retzius which, with the detachment and prolapse of the anterior wall of the bladder, had become enormously enlarged (Fig. 1). This space was roughly triangular or pyramidal in form, its base being formed by the prolapsed anterior wall of the bladder, its anterior boundary by the pubic rami, and its posterior face by the loosened peritoneum. A uterine sound, laid horizontally along the anterior wall of the bladder until its tip was stopped by the peritoneum, entered the cavity for a distance of from 6 to 7 cm. beyond the symphysis. The anterior (bony) wall and the posterior (peritoneal) wall of the space of Retzius were apparently of about the same dimensions as the base. This base, or floor of the space of Retzius, formed by the anterior wall of the bladder was paved with apparently healthy, bright red granulation tissue. The condition of epispadias involving the entire urethra exposed the red urethral mucosa of the posterior and lateral walls, and the internal sphincter region opened rather widely into the bladder. The index finger entered the bladder to the first joint, and with thumb and finger the retracted bundle of sphincter muscles could be palpated posteriorly. Anteriorly, palpation with thumb and finger showed considerable thickening of the anterior bladder wall next to the sphincter region, probably due to its recent repair together with the heavy layer of granulation tissue covering the entire anterior wall.

It was manifest that reconstruction of the urethra ought not be attempted until nature had been given time for such repair work as could take place. Accordingly, the patient was dismissed from the hospital, with instructions to return for observation at about monthly intervals.

The subsequent course of events can probably be made clear by quoting from our history records:

Oct. 15, 1935. Since returning home the patient has gained in strength and now looks well. The urine is retained perfectly for about two hours while she is lying down, but while on her feet she has no control. On examination the external urethra, the lateral walls of the urethra, and the entrance to the bladder appear about as formerly; but the large triangular area back of the symphysis, representing the space of Retzius, and formerly measuring about 6 or 7 cm. across each of its 3 walls, is now completely closed. Red granulation tissue overhangs the internal sphincter region, and on the right of the bladder opening there is a large protruding nodule of granulations.

Jan. 10, 1936. Patient looks well and says she is feeling well except for the incontinence. There is a moderate degree of cystocele and rectocele. The red, granulation masses seen in October as the final process in the filling in of the space of Retzius have now entirely disappeared and the infrapubic tissues are covered with epithelium,

I was asked to examine the patient on September 19, twenty days after the accident. For the previous week there had been partial continence, especially when the patient was lying flat in bed, the voidings amounting to about 200 c.c., but as soon as she assumed the erect posture there had been continuous leakage.



Fig. 1.—Sagittal view illustrating separation of bladder and urethra from pubic attachments. *A*, Retracted dorsal wall of complete epispadias. *B*, Opening into bladder. *S*, Retracted fibres of internal sphincter.

On examination with the patient in the lithotomy position, the outlet was fairly well lifted, and the introitus admitted two fingers easily. The levator muscles seemed well preserved. There was only a moderate degree of cystocele and rectocele. The cervix was somewhat prolapsed, but pointed about normally posteriorly. The fundus, in about normal involution, was sagging to some extent and occupied a position back of the normal axis.

The immediate repair of the inverted T laceration had healed satisfactorily over the portion involving the genital tract, but as regarded the urinary passages all the

the dorsal wall of the urethra, we attempted to pick up the ends of the internal sphincter muscle and bring them together across the dorsum, but all the tissues in the region of the sphincter ends were so infiltrated that we could not make a satisfactory suturing from side to side. We found that the tissues beside the urethra were more pliable and could be brought up over the sphincter region with sutures introduced up and down. Three No. 00, forty-day catguts were set in the vertical direction, and these reinforced with fresh tissues both the unsatisfactory sphincter closure, and the Lembert line along the dorsum of the urethra. After this further similar catgut sutures were taken in any direction that promised the filling in of prospective dead spaces.

Finally, the vaginal mucosa was brought together from side to side with interrupted black silk sutures. Because of the dearth of plastic vaginal mucosa in the vestibule, after all this region had been swept away from the symphysis, we were able to close the vaginal mucosa across only the lower half of the urethral tube. This left to be closed in by granulation a considerable triangular area measuring about 2 cm. on each of its three borders and lying over the internal sphincter region. However, as above described, we had been able to cover this sphincter area with a considerable amount of fresh tissue from beside the urethra, and it appeared that successful granulation might be expected before any tension would disrupt the sutures.

The small male urethral catheter was strapped to the inner thigh, and orders were given to irrigate the bladder twice daily with 200 c.c. of 1:1,000 silver nitrate solution and at the same time to flush the granulating area with about 100 c.c.

On the sixth day after operation the rubber drainage catheter came out and by the time the resident surgeon could arrive from the operating room to replace the catheter, 300 c.c. of urine had accumulated in the bladder without leakage.

On the twelfth day after operation some of the black silk sutures and on the seventeenth day the remaining stitches were removed. The vaginal flaps over the lower urethra had separated slightly in places because of tension, but the bared areas showed apparently healthy granulations, as did the large triangular area over the upper half of the urethra. The catheter was removed and instructions were given to put a commode beside the bed for use if the patient found that she could void more easily in the sitting posture than by using the urinal in bed.

In the hope of developing the remaining fibers of the internal sphincter muscle a course of treatments was instituted, in which the faradic electric current was applied for ten minutes each day over the sphincter region. This treatment was continued after she went home on March 1.

March 25, 1936. The patient says she is improving slightly but steadily. She has taken the electrical treatment daily except during four days of menstruation. She can control the urine at night for from four to five hours, and then awakens and voids without preliminary leakage. During the day, when she is about on her feet, she has practically no control. Occasionally she has a desire to void but never can pass more than one ounce. *Cystoscopy*: Knee-chest posture. Urethra takes Nos. 7, 8, and 9 Hegar dilators with a slight resistance to each. The Kelly speculum No. 8, when introduced, meets with definite obstruction as it goes through the internal sphincter region. The bladder mucosa appears normal. On withdrawal of the speculum the tissues of the internal sphincter region close about its end in a sluggish way as if the sphincter exerted no action. The urethra seems to be slightly longer than normal, measuring between 3 and 4 cm. The patient was advised to continue the electrical treatment daily for another month.

Oct. 23, 1936. The patient says she is leaking about as badly as ever. If she lies quietly on her back or side, it takes about three to four hours for the bladder to get full, but when she gets up to void, she leaks as soon as she assumes the erect posture. *Examination*: On separation of the labia the external orifice of the urethra

the portion which lines the epispadic urethra presenting a deep red color. The urethra has been drawn forward to a position somewhat nearer the symphysis. The large lateral labia of the external urethra show the orifices of the ducts of Skene's glands (Fig. 2). With the index finger in the bladder opening, one can outline on the floor of the sphincter region a large crescentic bundle of tissue probably representing the retracted sphincter muscles, but on asking the patient to contract these muscles no evidence of contraction can be felt.

Nature had solved our first problem, that of filling up the space of Retzius and drawing the bladder forward to its old position back of the pubic bones. Our second problem was concerned with the reconstruction of the urethral channel, and we decided to wait another month for further repair of the infiltrated tissues.

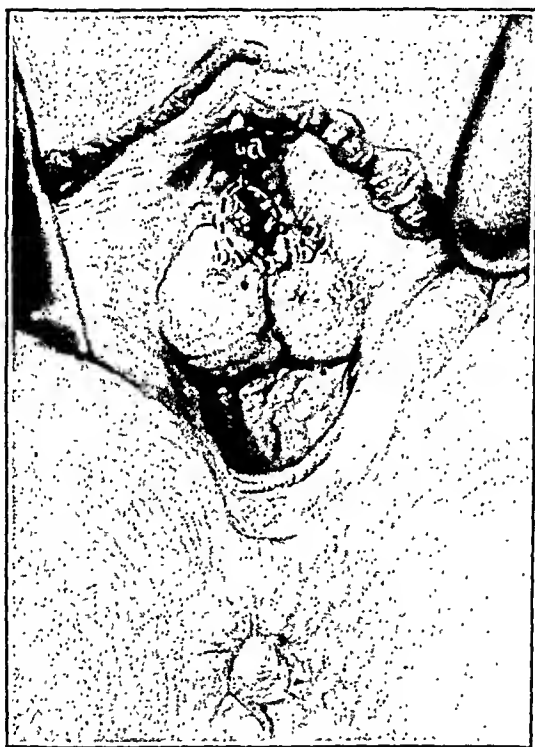


Fig. 2.—Incision for second operation, the reconstruction of the epispadic urethra.

Feb. 8, 1936. Patient readmitted yesterday, five months after her injury. While in the recumbent position, lying on her back or on either side, she is able to retain her urine for two or even three hours, but complete incontinence persists while she is on her feet.

Operation under avertin anesthesia supplemented with nitrous oxide gas. Repair of complete epispadias. A No. 9 male rubber catheter was inserted into the bladder and allowed to rest in the trough formed by the posterior and lateral walls of the urethra. An incision was made beneath the symphysis pubis, beginning in the midline next to the periosteum (Fig. 2, *a*). After carrying this downward about 15 mm. we met the upper edge of what was virtually a vesico-urethrovaginal fistula. The incision was then divided and carried down the outer edge of the urethral mucosa on either side (Fig. 2, *b*). The urethral mucosa was then carefully dissected away from the vaginal mucosa on both sides. With a continuous Lembert suture of No. 2 plain catgut, we began at the upper end and brought together, back to back, the two edges of urethral mucosa down to the external orifice. After the Lembert suture, to restore

From the nature of the urethral injury which had completely severed all the fibers of the internal sphincter region, allowing them to retract to the inferior arc of the sphincter circle, it was probable that no form of puckering or shortening of

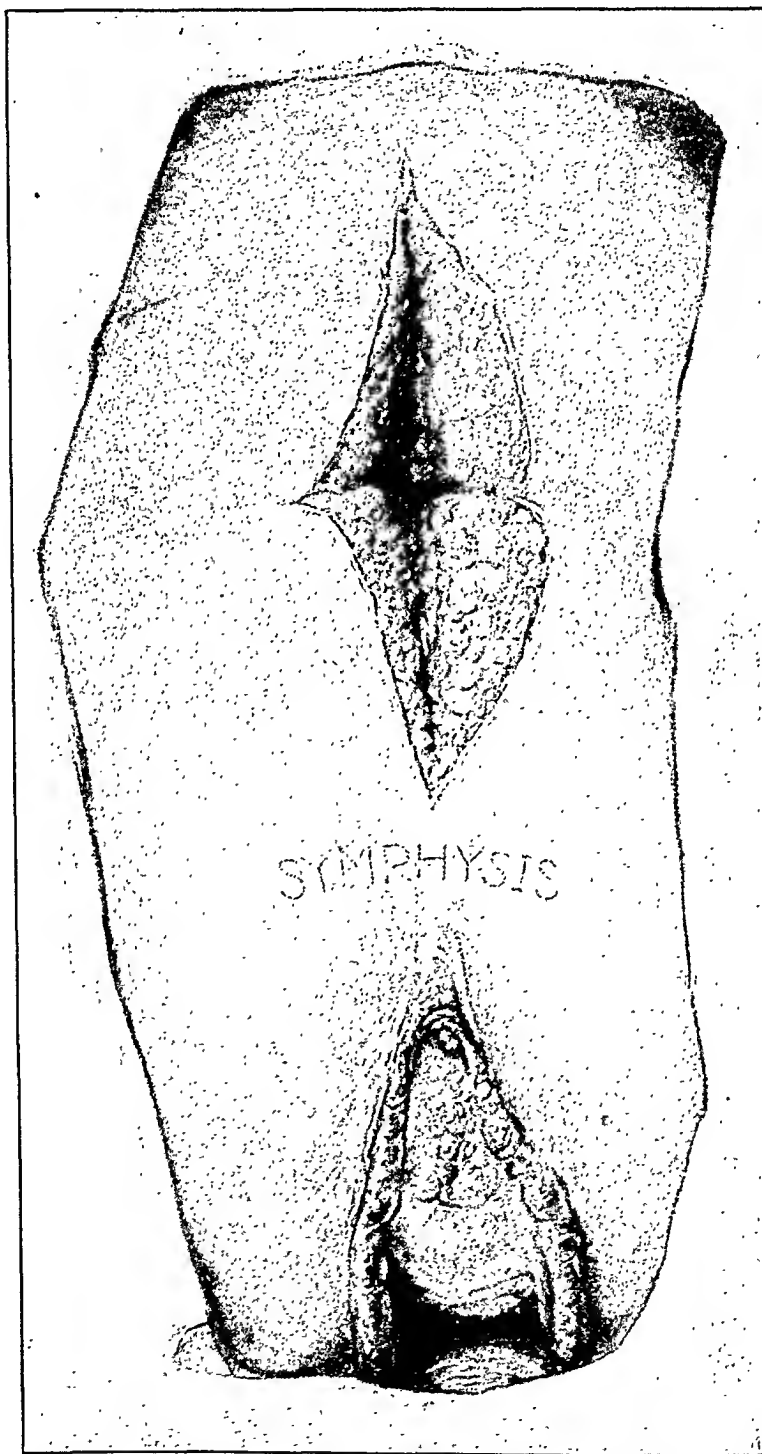


Fig. 4.—Illustrating draping of patient preliminary to the fourth and final operation.

these muscles by a suburethral approach would have restored their function. Success was rendered more unlikely because of the probable destruction of the chief nerve supplies to all portions of the urethra, the original injury manifestly having destroyed

was still found to sag posteriorly at a distance of about 2 cm. from the arch of the symphysis (Fig. 3). We decided to see whether elevating the external urethra and bracing it up in a more normal position against the symphysis might improve the degree of continence.

Third operation: On October 26 the patient was given by rectum a small dose of avertin and this was supplemented with nitrous oxide anesthesia. A diamond-shaped area of tissue was laid bare, each side measuring about 15 mm. With a small staphylorrhaphy needle and No. 32 virgin silver wire, the mucosa in the upper



Fig. 3.—Incision for third operation, an attempt to draw the external half of the urethra closer to the symphysis.

edge of the external urethral orifice was transfixed, carried to the upper angle of the bared area, and the suture set through the periosteum and mucosa beneath the symphysis. The lateral edges were brought together with sutures of fine black silk. A No. 10 male rubber catheter was kept in the bladder for three days after which it was removed and the patient allowed to use a commode.

By the end of the eighth day the silver wire and some of the black silk sutures had cut through, but the healing had been fairly satisfactory. However, the external orifice had not been permanently drawn forward for more than half the distance we had anticipated, and the final result had not appreciably improved the patient's control of her bladder.

above and carefully dissecting the flap downward to the region of the symphysis. This flap contained a small bundle of fibers from the median edge of each rectus muscle. When we reached the upper ends of the pyramidalis muscles, we carefully

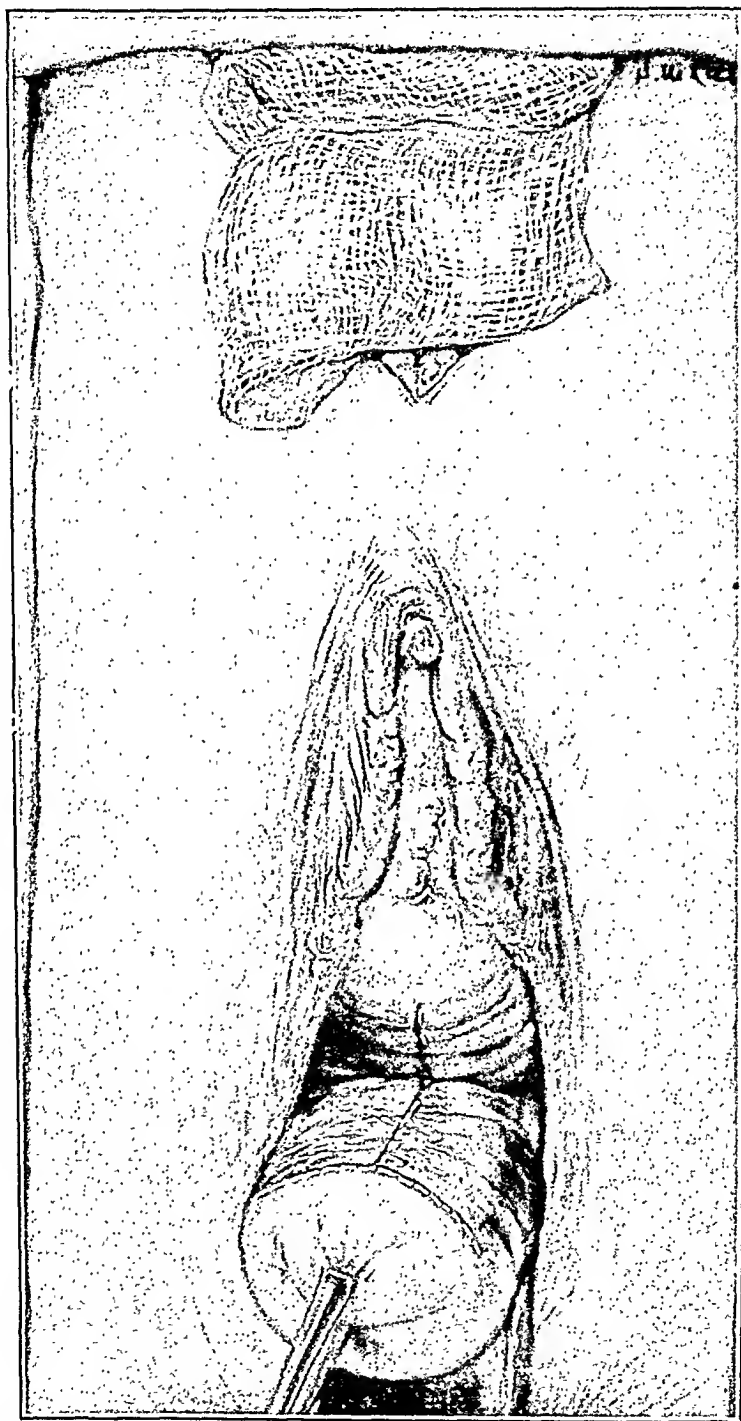


Fig. 6.—Incision for exposure of the suburethral space for reception of the pyramidoplasty straps, and for interposing the uterus beneath the bladder.

worked more deeply, so as to keep beneath these muscles and bring them along with the flap. Then holding the flap in a vertical position we cut down along its midline in order to form two fasciomuscular flaps. These flaps were dropped in the lower end of the wound and covered with gauze wet with salt solution. The upper portion

much of the involuntary internal sphincter or trigonalis muscle, and much of the voluntary muscles, with their nerves, derived from the urogenital diaphragm and the bulbocavernosus.

This situation seemed to call for a transplantation of muscle, and the most promising method appeared to be the Miller¹ modification of the Goebell-Stoeckel pyramidoplasty.

Fourth operation: Jan. 10, 1937. *Avertin, gas and ether anesthesia. Restoration of urethral control by modified Miller-Stoeckel pyramidoplasty, cure of cystocele by interposition operation, cure of rectocele by plastic repair of levator ani muscles.*

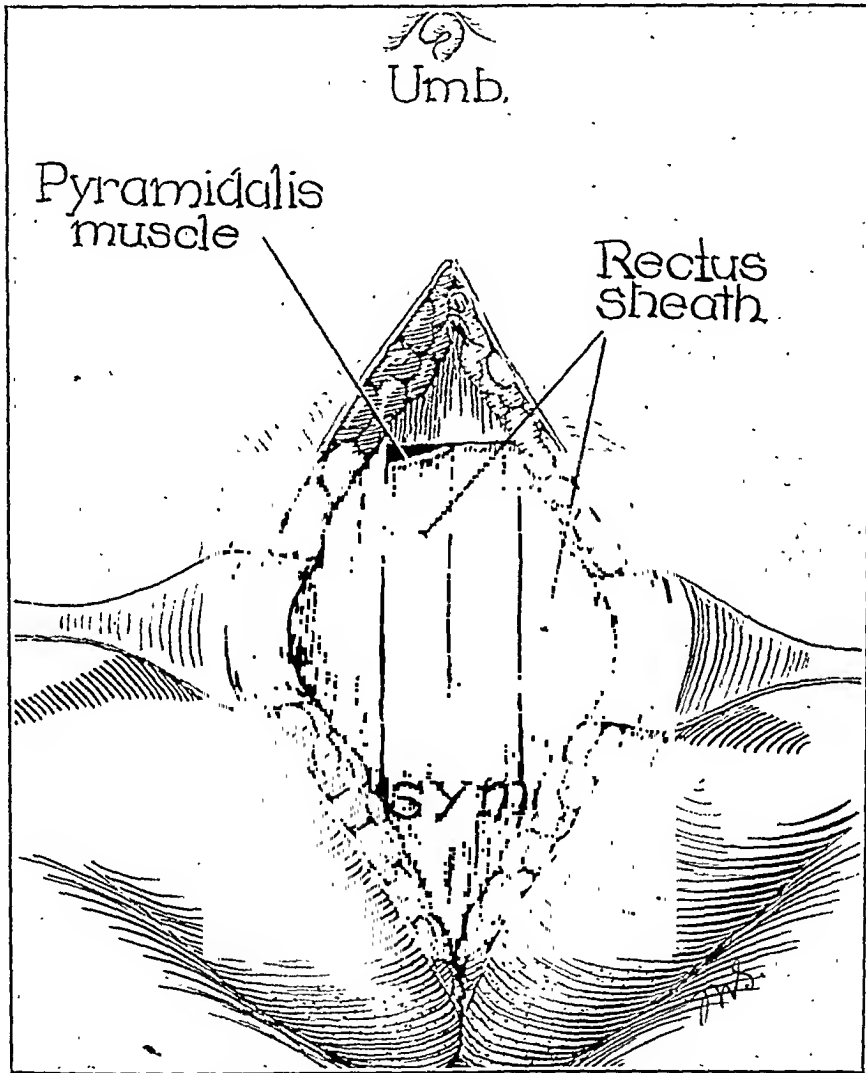


Fig. 5.—The strip of fascia with subadjacent pyramidalis muscle is cut and divided longitudinally.

The patient was placed in a modified lithotomy position and draped so that the entire operation could be done without change of position on the table. A midline incision was made, extending for two-thirds of the distance between the symphysis and navel (Fig. 4). Blunt dissection of the fat in the anterior wall from the deep fascia over the rectus muscles. At a point about one-third the distance below the navel we made a small transverse incision across the midline, this incision through the fascia of the rectus being almost 2 cm. long (Fig. 5). A vertical incision was carried from each end of this transverse incision down to a point about 1 cm. from the symphysis. We then lifted this entire flap from the rectus muscles, beginning

beginning near the external urethral orifice and encircling the anterior aspect of the cervix (Fig. 6). We next lifted up triangular flaps of the anterior vaginal wall, beginning at the cervix and working upward, freeing the vagina from the bladder. As we reached the region beneath the urethra there was a good deal of old scar-tissue resulting from the childbirth injury. We were careful to keep close to the vaginal submucosa and avoid any remnants of muscle of the urethral sphincter that might be left.

The peritoneal cavity was then entered in front of the cervix and the bladder freed from the uterus and the tissues of the base of the broad ligaments. A wet gauze open sponge was pushed into the depths of the wound on the anterior wall of the uterus.

Next we brought down the rectus flaps and crossed them beneath the urethra (Fig. 7). The tissues alongside of the urethra and beneath the pubic arch were dense and almost of a cartilaginous character, and it seemed best to avoid exposing them with an open incision. The fat of the mons veneris was thick and an incision through it would have added to the dangers of postoperative wound infection.

For these reasons we modified the Miller method which extends the abdominal incision downwards through the Mons and through one labium majus and labium minus and connects with the suburethral incision. We simply took a curved Kelly clamp and beginning opposite the middle of the urethra we inserted the clamp first toward the right side, keeping close to the deep fascia over the pubic bone and directing the clamp upward. Its tip came out above the pubes in the lower end of the original abdominal incision. The clamp grasped the right rectus flap and dragged it back through this tunnel and then dropped it with its former upper end resting beneath the urethra. The same procedure was carried out on the left side. We found that our flaps were about 3 cm. longer than was necessary for allowing them to meet in the midline beneath the urethra (Fig. 8, *a*). We crossed the flaps in the form of an X, attaching first their upper edges together and taking up a bite of the suburethral tissues, after which the lower edge of the X was fastened in the same way to the suburethral tissues at a slightly higher point on the urethra (Fig. 8, *b*). This was done with fine linen thread. Then the redundant ends of the flaps were fastened to the subpubic tissues on either side, the flaps thus making a complete cross beneath the urethra (Fig. 8, *c*).

We then tested the effect on the urethra by passing a Kelly clamp into the urethral canal. Earlier in the operation any pressure on the bladder had caused the urethra to leak freely with urine, and a Kelly clamp would drop into the bladder almost of its own weight. But, now a Kelly clamp when being introduced into the bladder, met a distinct obstruction about midway in the urethra and had to be manipulated and slightly pushed before it would enter. We then tried an ordinary glass catheter and this met with a distinct obstruction as it passed through the urethra. A large quantity of urine drained off through the catheter.

The gauze drain, which had been pushed into the peritoneum, was now removed. The uterus was grasped on its anterior wall with tenaculum forceps and drawn forward through the peritoneal opening. With the index finger the uterovesical edge of peritoneum was pulled into the wound and attached on the anterior aspect of the dome of the uterus. Then the uterus was brought snugly forward beneath the urethra by two interrupted twenty-day catgut sutures going through the edge of the vaginal wall, grasping the anterior face of the uterus and coming out through the opposite edge of the vaginal wall.

We then trimmed off a triangle of excess vaginal wall on either side just anterior to the cervix and finished closing the anterior vaginal wall with interrupted twenty-day catgut sutures, each grasping the anterior face of the uterus and cervix as we worked downwards. Between the lower interrupted sutures a one-inch iodoform

of the abdominal wound was closed by bringing the rectus muscles and fascia together in the midline with whipped interrupted twenty-day No. 2 chromic catgut. Then several No. 2 plain catgut sutures closed the fat layers. Next, beginning at the upper end of the wound, a subcutaneous silver wire suture was used to close the

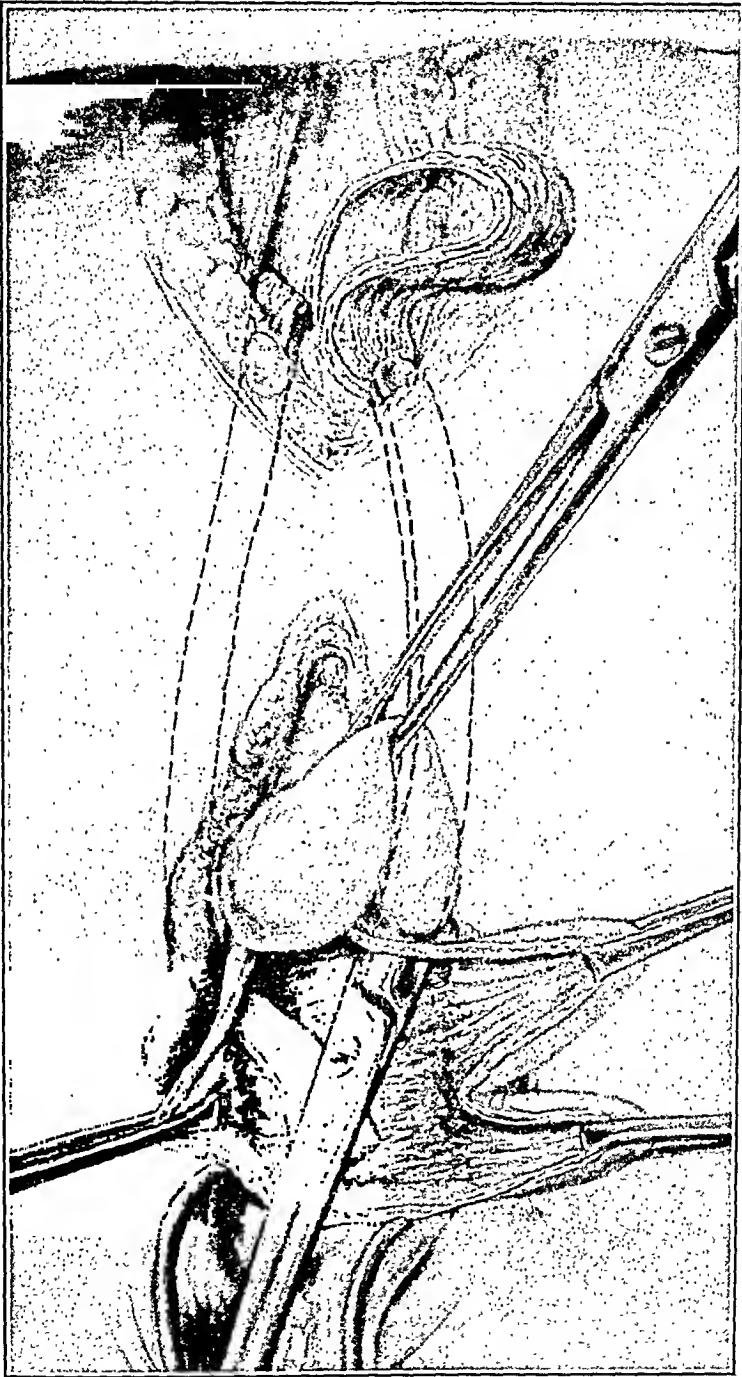


Fig. 7.—Pyramidoplasty straps being drawn through the subcutaneous tunnels to the suburethral space.

skin down to a point about opposite the upper ends of the pyramidales. From the perineal approach we performed the interposition operation which was meant to do away with the cystocele and to bring up the fundus snugly beneath the urethra. Grasping the external end of the urethra with Allis clip and the cervix with the four-prong tenaculum we carried a midline incision down the anterior vaginal wall,

Postoperative History.—Convalescence was prompt, all the wounds healing normally. The urethral catheter was removed at the end of one week, after which the patient had perfect control up until the nineteenth day, when there was a slight unexplained leakage after she had been about the ward in a wheel chair for about two hours.

About ten days after the operation the patient complained of pain and soreness in the region of the left kidney. This reminded her of attacks she had had two or three years previously, particularly after getting her feet wet or catching cold. On

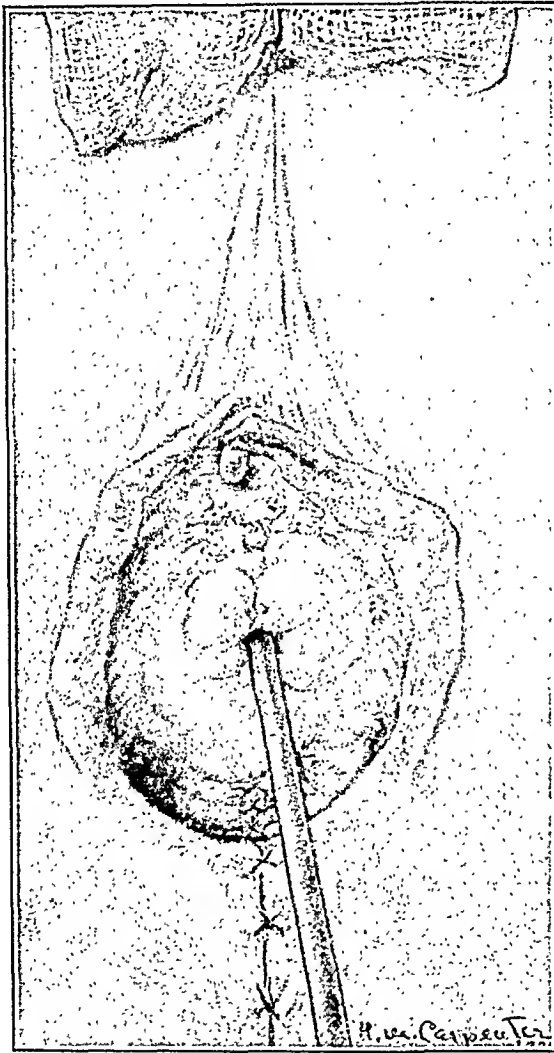


Fig. 9.—Final closure of operative wounds. Male catheter to be strapped to the inner thigh.

several occasions during our studies of her case she had complained of abdominal and pelvic pains which led us to suspect the presence of bilateral ureteral stricture, and on each of these occasions examination revealed tenderness over the ureters in the pelvic brim and broad ligament regions. On Feb. 8, 1937, a two-hour intravenous phenolsulphonephthalein test showed 1,000 c.c., 75 per cent of dye; blood pressure 105/80; Hb 85 per cent; white blood cells 6,360. Urinalysis, 1,005, acid, sugar 0, albumin 0; micro. 0. Culture from bladder, gram-negative bacillus, colon group.

A test of the left ureter with a No. 11 Fr. bulb near the catheter tip revealed apparent stricture in the upper ureter and again in the broad ligament region. A test of the right ureter on February 10th showed stricture in the broad ligament region.

gauze was placed in the broad ligament spaces on the anterior face of the cervix to offer temporary drainage.

The moderate rectocele was then repaired by making a transverse incision on the lower edge of the fourchet and dissecting up the posterior vaginal wall from in front of the rectum to expose the edges of the levator ani. These edges were brought together in the midline with a figure-of-8 of twenty-day catgut. Then a twenty-day catgut was used as a crown suture. Before tying this crown suture, we

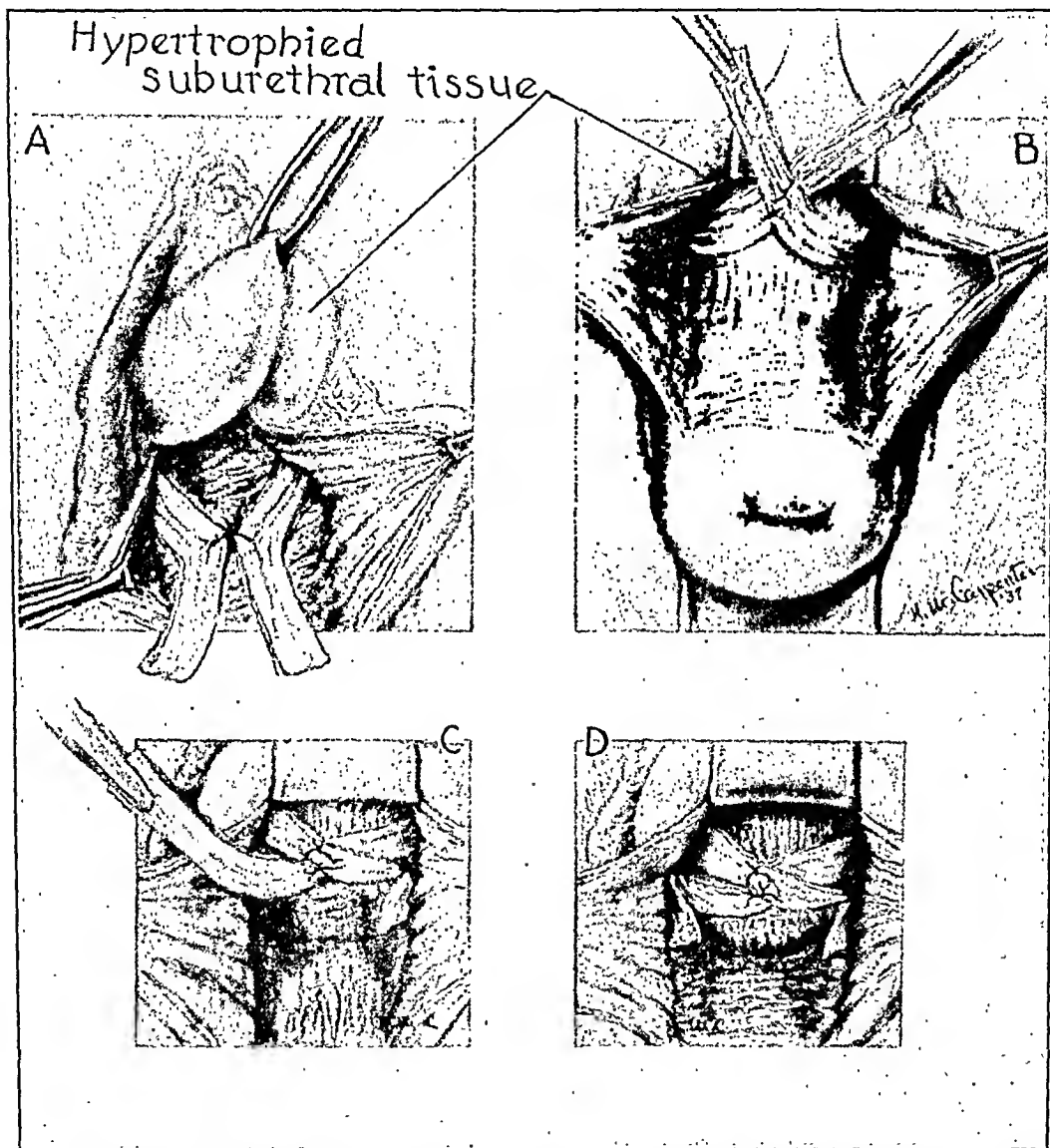


Fig. 8.—Straps crossed beneath the urethra, and outer ends fixed to the subpubic periosteum.

set three plain catgut sutures through and through from the sides, picking up the floor of the perineal body to close all dead spaces. These were first tied, and last of all the crown suture.

The iodoform gauze draining the broad ligament spaces was brought out to the vulva and plain sterile gauze was packed beside it in the vaginal channel. Both these gauzes were to be removed on the third day. A No. 9 male catheter was passed into the bladder and strapped on the inner side of the thigh for permanent drainage of the bladder (Fig. 9). The operation was completed by closing the lower end of the abdominal incision.

DISCUSSION

DR. NORMAN F. MILLER, ANN ARBOR, MICH.—The paper lends itself to discussion from two points of view, first the obstetric and second the gynecologic. Such tremendous trauma as a result of spontaneous birth seems most unusual. I am led to ask whether any use was made of a powerful stimulant, such as pituitrin? I have seen one example of trauma of this extent. This occurred in a young woman as a result of a horseback accident. The girl suffered an injury very similar to the one described by Dr. Hunner.

In some similar cases, not with such extensive trauma, we have corrected the incontinence by various means, by repair of the anterior vaginal wall, and occasionally by the interposition operation. Where we have failed by one method or another we have resorted to a modification of the Goebell-Stoeckel operation. During the past six or seven years we have used it a number of times. We have constantly changed the technique. The difficulty reported by Dr. Hunner has also occurred in our experience and we have changed from the original modification as reported by me in 1931. I believe this operation has much to recommend it in occasional cases.

I believe that we as gynecologists must seriously consider the problem of restoring urinary control in women afflicted with this difficulty. It is surprising the number of individuals who complain of varying degrees of incontinence, particularly older women.

DR. GEORGE GRAY WARD, NEW YORK, N.Y.—I have had a similar case of lack of control which I successfully cured by utilizing a procedure used abroad a good deal with success and known as the Martius operation. It is simpler than the operation Dr. Hunner used. The bulbocavernosus and ischiocavernosus muscles which fuse together in a common tendon near the clitoris are severed at that point, and the two united muscles are brought under the reconstructed urethra and attached to the opposite pubic ramus. In some instances the muscles of both sides are used. This has given very satisfactory results.

Dr. Miller stressed the fact that so many women have incontinence when sneezing or coughing. That is a very common condition. Dr. Kennedy of my staff has been making some interesting studies with the x-ray to show the muscular control of the urethra and has devised a procedure which is under trial and which has been successful in some cases.

DR. HUNNER (closing).—I have no explanation of how this accident happened. The patient had had no drugs to hasten labor. I assume that the head was engaged so long that there had been injury from pressure on the tissues posterior to the symphysis, making it easy for the head or shoulders to sweep them down at the time of birth.

The use of the vaginal muscles did appeal to me very strongly in this case, but the left bulbocavernosus was cut across in the original injury destroying its upper third at least, and I was very much afraid that probably both of them had been pretty well detached from their nerve supply and were not particularly available in this case.

To use fascial straps from muscles having an uninjured nerve supply seemed safer, and in this case, with its sagging urethra, the symphysis arch offered a counterpoint of pressure for the tension of the pyramidalis straps.

The urine from each kidney was negative for leucocytes but on a slant agar tube there grew numerous colonies identified as belonging to the colon group.

A grip epidemic was prevalent in Baltimore at this time and the patient had a slight head cold at the time of our investigation of the ureters. The day after our last investigation her temperature reached 102.8° and this was thought to be due to a moderate left side pyelitis following the ureteral trauma in the presence of a renal bacilluria. However, on February 12 and 13 the temperature ranged between 101° and 105°, and there were typical signs of moderate consolidation in the left lung. There was slight loss of urinary control during these two days of high temperature. Blood cultures were negative. The temperature reached normal on February 16, but registered 102° on February 20 and at this time there were signs of acute pharyngitis and malar sinusitis. The temperature remained on the normal line from February 26 until the patient's dismissal on March 6. During the final days of hospital convalescence the patient, while sitting, or walking about the ward, had occasional slight leakage but controlled this promptly by contraction of the abdominal muscles.

She returned at our request on April 12, and reported that during her first week at home there was occasional slight leakage which she could readily control. A few days later she lifted her 32-pound boy and felt something give way in the region of the pelvis and after that she had no real control. At night she retained the urine for about four hours and then awakened spontaneously and voided without loss of control, but while at her housework in the daytime she had to wear a pad and did not void voluntarily at any time.

I had neglected to warn the patient against coitus for a definite period after returning home, and my first thought after hearing of the failure of the operation was that the pyramidoplasty straps may have been broken down during coitus. The patient stated, however, that coitus had not been resumed until after the bladder control had been lost. I believe that control can be restored by the comparatively simple operation of exposing the field beneath the urethra and then dissecting out and shortening the fascial straps.

Reference to Fig. 8 shows that the straps at their point of crossing were fastened together by two linen sutures, each of which was attached to the suburethral tissues, and that the end of each strap was then fixed to the deep fascia beneath the pubic bone. In a future operation I plan to detach the straps at the X crossing and carry each one independently across to its fixation in the subpubic fascia. Each strap will be shortened and given as snug a lift against the urethra as seems feasible. By this method it is quite conceivable that if an accident were to happen to one strap, the other would continue to function with complete control.

When last seen on May 7, the patient expressed the desire to wait until October for another operation. This conformed with my wishes, for plastic work about the urethra or bladder should not be attempted at too short intervals. This also gives ample time for a few more ureteral dilatations which will mean much for the patient's future health.

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Such detail classification is unnecessary in routine diagnosis. Hopkins and Hesseltine⁴ found atypical fermentation in a few strains of monilia and, therefore, suggested that both the cultural reactions and microscopic morphology be utilized where monilial strain identification is desired. They concluded also that since organic acids were unknown as end-products the difference between acid or acid and gas in sugar fermentation represented only a difference in degree. Moreover, the size of the inoculum may alter these reactions appreciably. Fig. 1 shows degrees of gas production.

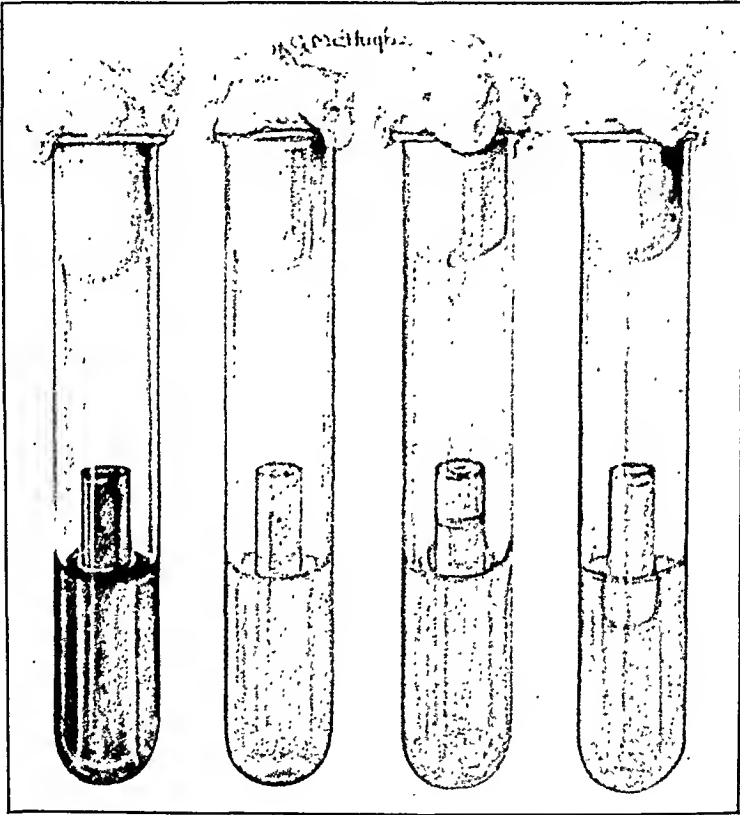


Fig. 1.—Fermentation tubes with bromcresol purple indicator. Tubes one to four read from left to right. (1) No fermentation. (2) Acid but no gas production. (3 and 4) Show different degrees of gas production.

PATHOGENICITY

Plass, Hesseltine and Borts⁵ reviewed the literature up to 1931. Their own data indicated that pregnancy and diabetes mellitus were predisposing conditions for mycotic vulvovaginitis, and demonstrated convincingly that the sporadic oral thrush in the newborn was in all likelihood the result of contamination from its mother's fungus-infected vagina. Their description of the clinical appearance, symptoms, and diagnostic methods is complete. In 1934 by fulfilling Koch's postulate these teachers⁶ proved that these organisms were pathogenic. It was stated then (and the importance was stressed) that certain patients of the experimentally inoculated group failed to develop the disease, even

BIOLOGIC AND CLINICAL IMPORT OF VULVOVAGINAL MYCOSES*

H. CLOSE HESSELTINE, M.S., M.D., CHICAGO, ILL.

(From the Department of Obstetrics and Gynecology, The University of Chicago, and The Chicago Lying-In Hospital)

PATIENTS are primarily interested in the relief of distress. While progressive physicians are interested in symptoms, they are concerned with the improvement of diagnostic and therapeutic methods as well as a better understanding of the entire disease process. Although the yeast-like fungi (monilia and cryptococci in particular) have long been recognized as etiologic agents of vulvovaginal mycosis, the frequency of the disease, predisposing conditions, improvements in therapy, and mode of action of the organisms have been more completely investigated recently. Perhaps through a better understanding of the biologic action of these organisms one may find avenues for approaching other problems. Only the monilia and cryptococci are under consideration here, though the terms oidium and torula, respectively, are at times incorrectly substituted.

CLASSIFICATION AND IDENTIFICATION

The total number of the yeast-like strains with pathogenic propensity is still unestablished. Furthermore, the taxonomy is chaotic. The term monilia as used here includes those strains known by Benham¹ and others as *M. albicans*, *M. candida*, etc., or by Stovall and Bubolz² as Type 1, 2, and 3. Because endomyces and saccharomyces are discussed in the current literature along with the monilia and cryptococci, Table I may aid in dividing these groups. Monilia develop mycelia and conidia but no spores, while cryptococci have conidia only and no spores. The conidia appear within twenty-four to forty-eight hours in Sabouraud's culture medium. Mycelia may not develop for days on this medium and infrequently special media with prolonged incubation may be required to bring them out. Likewise, ascii or endospores of endomyces and saccharomyces may develop slowly even upon special media. Benham,¹ and Benham and coworkers,³ Stovall and Bubolz,² and others have described these procedures fully. The former group of investigators recommend the giant colony and microscopic appearance for identification, while the latter urge the use of the cultural characters in galactose, saccharose, lactose and calcium milk especially for the types of monilia.

*Read at the Sixty-Second Annual Meeting of the American Gynecological Society, held at Swampscott, Mass., May 31 to June 2, 1937.

are symptom free. If specific infections, as gonorrhea and trichomoniasis, are excluded, the relationship between symptoms and positive cultures is even more striking.

The incidences in the nonpregnant series are comparatively low, varying from 7 to 16 per cent. The Health Service group included only those with special complaints while the clients of the Douglas Smith Foundation were generally normal women. The deviation might be explained in part upon economic and hygienic levels, particularly since Todd¹⁰ found 18.2 per cent of normal women harboring *M. albicans* in the mouth and throat and Benham and Hopkins³ found 80 per cent of normal individuals to have yeast-like organisms in the mouth and feces.

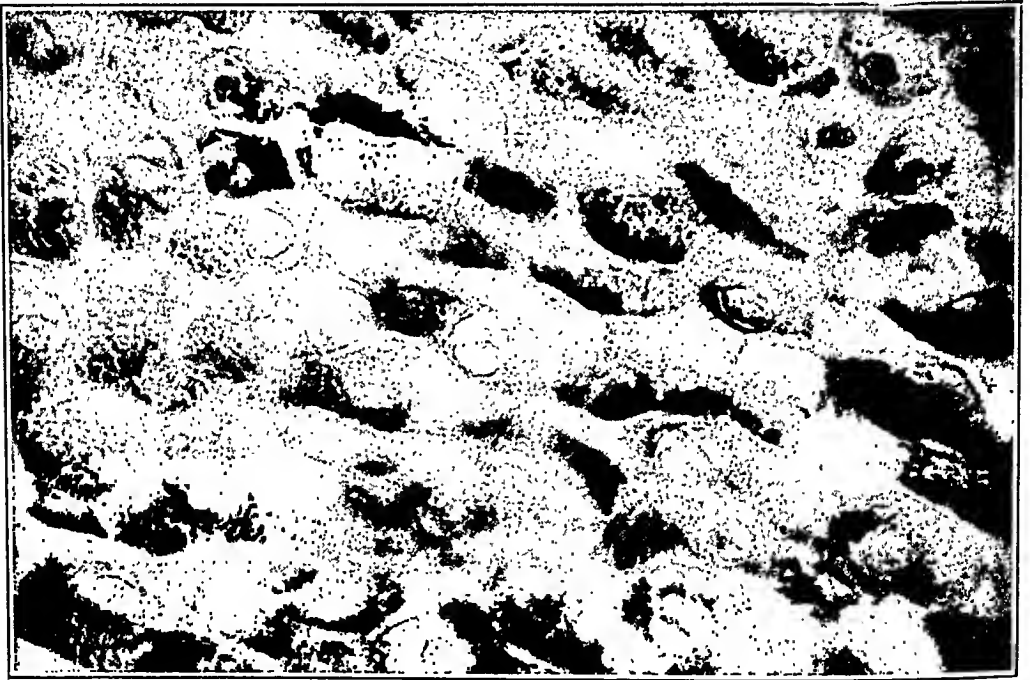


Fig. 2.—Glycogen-like material in vaginal epithellum demonstrated by Best carmine stain. $\times 1200$. (After Adair and Hesseltine.)

Other sources of fungus infection, as the husband, clothes, or instruments, seem less likely.

INFLUENCE OF CHANGES IN THE VAGINAL EPITHELIUM

Adair and Hesseltine,¹¹ Karnaky,¹² Davis and Pearl,¹³ and others have demonstrated the increased glycogen-like material in vaginal epithelium during pregnancy. The amount of this cellular content may be estimated microscopically when the biopsy specimen is fixed in absolute alcohol and stained according to the Best carmine technic. Fig. 2 shows a magnification of several hundred times and is self-explanatory. This increased source of carbohydrate, since it produces apparently a more favorable environment, may logically explain the increased incidence of fungi in the vagina. Conversely, the sudden loss of this material at

though the organism might be harbored for a considerable period. This observation supports the view that mycotic carriers do exist. So far, endomyces have not been definitely found in the vagina, and saccaromyces are supposed to be nonpathogenic.

TABLE I. MICROSCOPIC MORPHOLOGY

	MYCELIA	CONIDIA	ENDOSPORES
Monilia	Present	Present	Absent
Cryptococci	Absent	Present	Absent
Saccharomyces	Rudimentary only	Present	Present
Endomyces	Present	Present	Present

Differential Cultural Characteristics

Monilia		GALACTOSE	SACCHAROSE	LACTOSE	CALC. MILK
Type I	Stovall & Bubolz	Acid	Acid	0	0
Type II		Acid gas	Acid	0	Coagulation
Type III		Acid gas	Acid gas	0	0
Endomyces		Acid gas	Acid gas	Acid gas	0
Cryptococci		0	0	0	0

INCIDENCE

Table II presents a varied incidence of fungi in the adult human vagina. The patients of Plass and others⁷ at the University of Iowa were mostly indigents from rural communities. In contrast, the patients studied by Woodruff, Hesselstine and Phillips^{8, 9} at the University of Chicago were almost solely urban. The incidences in the obstetric patients varied in Chicago from about 15 per cent at the Chicago Lying-in Clinic to 41 per cent in the colored patients at one of the Chicago Lying-in dispensaries. The white patients at this same dispensary had 33 per cent positive cultures, a frequency not much lower than in the University of Iowa series. Positive cultures are found far more commonly in patients complaining of vulvar irritation than in those who

TABLE II. INCIDENCE OF FUNGI IN PREGNANT AND NONPREGNANT PATIENTS OF VARIOUS TYPES

	PREGNANT			NOT PREGNANT		
	TYPE OF PATIENT	TOTAL CASES	POSITIVE CULTURES	TYPE OF PATIENT	TOTAL CASES	POSITIVE CULTURES
Plass, Borts, Hesselstine (S.V.I.)	Hospital ward	232	87 (37.5%)	Hospital ward	320	35 (11%)
		48 vulval irritation	27 (56.0%)		118 vulval irritation	21 (18%)
		184 no irrit.	60 (32.0%)		202 no irrit.	14 (7%)
Woodruff Hesselstine Phillips (U. of C.)	Lying-in Hospital	152	22 (14.5%)	Univ. Health Service	37	6 (16%)
	Stockyards (white)	150	50 (33.0%)	Douglas Smith Found.	73	8 (11%)
	Stockyards (colored)	100	41 (41.0%)			

INFLUENCE OF GLUCOSE

If glucose did directly produce this tissue reaction, the clinical picture could be duplicated by washing the vulva with glucose solution (Table III). Consequently, nine patients free from vulvovaginal fungi and without local disease received 250 c.c. of a 10 per cent glucose (aqueous) solution as a vulval irrigation 5 times daily. These treatments were



Fig. 4.—G. S. 79243. Diabetic patient with mycotic vulvitis involving the introitus, labia minora and medial aspect of labia majora.

given for three to twenty-two days (average ten) and in not one did symptoms develop or the tissue change. Five patients with mild vaginal mycosis or with fungi present in the absence of symptoms received the same treatments for one to five days (average three). All five of these women either developed a vulval mycosis or had the symptoms of an existing mycosis aggravated.

parturition leaves a less favorable environment and accounts for the sudden loss of symptoms. Peculiarly enough, immature girls are not known to have vaginal mycosis, and postmenopausal women rarely develop this disorder. The fact that glycogen-like material is present in lesser amounts in the premenaeic and postmenaeic vaginal epithelium lends additional support to the idea that its presenece or absence is associated with an increase or decrease, respectively, in the mycotic infections. Adair and associates^{11, 13} have described the histopathologic picture of the vaginal epithelium in normal patients and in those with mycosis, trichomoniasis, and senile vaginitis.

INFLUENCE OF DIABETES MELLITUS

One of the complications of diabetes mellitus in adult females has been a condition called "diabetic vulvitis." It is still stated by many that the glucose or irritating substances in the urine are responsible for the

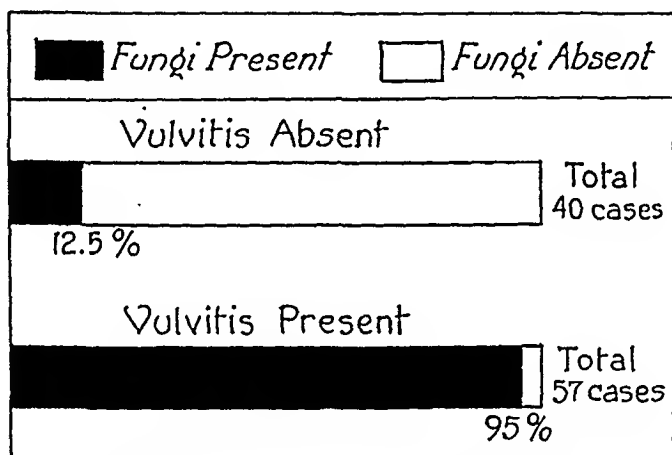


Fig. 3.—Incidence of fungi in diabetic women.

tissue reaction. The data of Plass and coworkers,⁷ and Hesselstine's and Campbell's¹⁴ are pooled to illustrate better the incidence of monilia and cryptococci. In all, 97 adult diabetic patients were cultured by the usual method for fungi (Fig. 3). One group consisted of 40 adult patients without vulvitis and only 5, or 12.5 per cent, had yeastlike organisms, an incidence about equal to that in the average group of nonpregnant women. On the other hand, 54, or 95 per cent, of the 57 with vulvitis netted positive cultures. One of the 3 negative patients was menstruating and the other 2 had used local medications before coming to the clinic. Unfortunately an opportunity for repeating these cultures did not occur.

The clinical appearance of this entity varies moderately, and at times may resemble certain stages of kraurosis (Tausig¹⁵) or chronic atrophic dermatitis (Adair and Davis¹⁶), although neither of these pictures (Figs. 4 and 5) illustrates this similarity well. Because a few diabetic females develop vulvitis and seek relief, it is imperative that the former disease be excluded in every patient suffering from mycotic vulvitis.

TABLE III. TISSUE REACTIONS OF VULVA AND VAGINA TO GLUCOSE IN NONDIABETIC WOMEN

DOSAGE	FUNGI	DAYS TREATED		TISSUE CHANGES OR SYMPTOMS
		PER PATIENT	AVERAGE	
125 grams daily wash	Absent (9 cases)	3-22	10+	None
125 grams daily wash	Present (5 cases)	1-5	3-	Increased or induced mycosis
Glucose powder	Absent (4 cases)	7-21	12	None
Glucose powder	Present (5 cases)	2-7	4+	Increased or induced mycosis

THERAPY

When the patients can receive vulvovaginal topical application 3 to 6 times a week, good results are obtained by using 1 or 2 per cent aqueous gentian violet solution as recommended by Plass and others.⁵ Karnaky¹² advocates the use of a 5 per cent gentian violet in an alcoholic vehicle. The Chicago Lying-in Clinic patients object to such alcoholic concentration and often are unable to make frequent trips for local treatment. Several types of medicated douches failed to cure or even give much relief.

According to Hesselstine and Noonan,¹⁷ beneficial results from acid and alkaline douches are highly improbable since these fungi tolerate pH ranges from 2.5 to 8.5 with increased cell growth. Even at a pH level of 9.5 the fungi were not destroyed promptly (Table IV).

TABLE IV. COLONY COUNT AFTER TWENTY-FOUR HOURS IN POURED PLATES (INOCULATIONS FROM TWENTY-TWO-HOUR GLUCOSE BROTH CULTURES). AVERAGE OF DUPLICATE TUBES. EACH 0.02 C.C. HAD 200 CELLS IN ORIGINAL INOCULATION

pH	F40	104	119	120	147	149	152	155	156	157
2.5	5,570	406	436	α	821	α	628	12	424	α
5.5	α*	α	α	α	α	α	α	α	α	α
7.5	-	α	3,904	-	α	-	α	2,745	α	-
8.5	72	α	1,384	α	α	α	α	2,170	2,500	1,700
* = not run α = innumerable (After Hesselstine and Noonan.)										

Hesselstine and Hopkins^{18, 19} studied 86 materials for fungicidal potency. The following general groups indicate the comprehensive nature of the study: 11 acids, such as picric and salicylic; 10 dyes; 24 halogens, as element and combined iodines, organic and inorganic chlorine; 23 other metallic compounds, as arsenicals, mercurials, etc.; 11 other organic substances, as cresol, thymol, etc.; and 7 vehicles. When human serum and cells were added to the test solutions only a few substances warranted further study. By testing the fungicidal action on several yeastlike strains, element iodine was demonstrated to be the most potent and consistent agent. This confirms the reports of Emmons,²⁰ and Woodward, Kingery and Williams.²¹ However, iodine as such is too irritating in the necessary dosage for vaginal therapy. Dieckmann and Hesselstine²² found the liberated iodine from potassium iodide

Another series was then treated by inserting 4 to 8 gm. of glucose into the vagina daily. Four fungus-free patients were treated seven to twenty-one days (average twelve days) without producing symptoms or tissue alteration. Five fungus carriers received the same treatment for two to seven days (average 4+ days), and every one had either an increase in severity of mycotic symptoms or induction of mycosis.

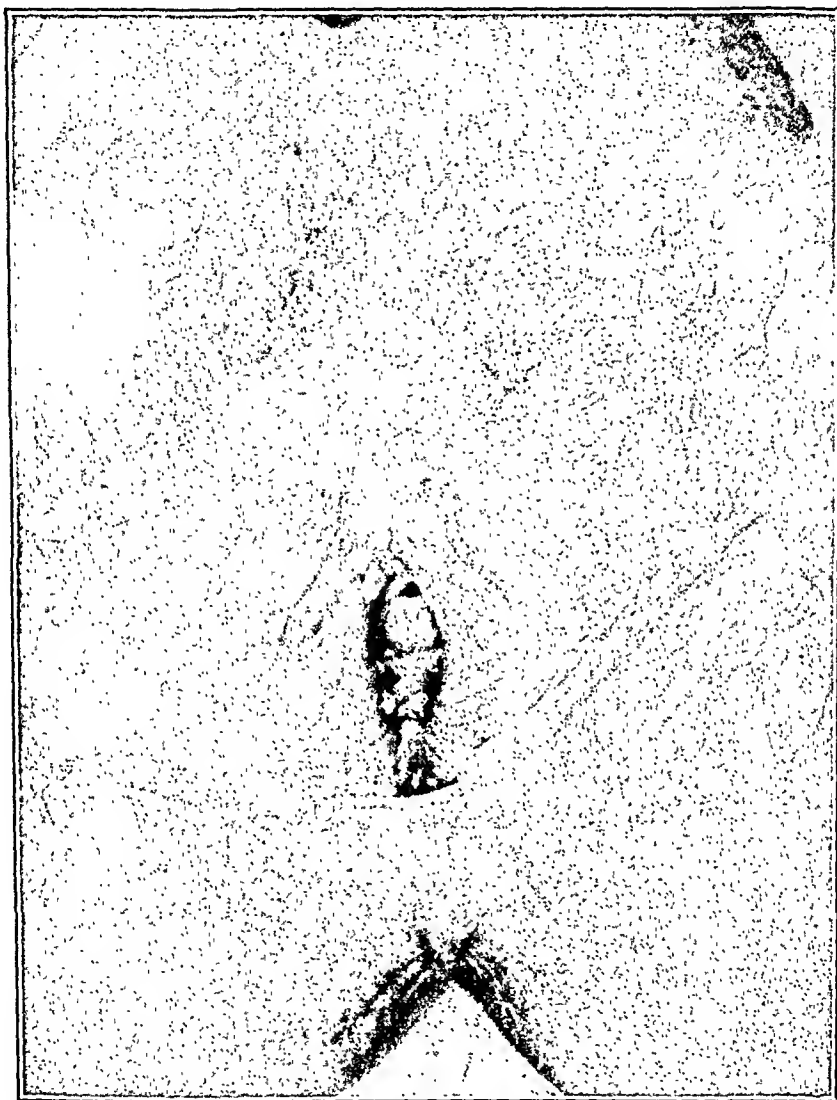


Fig. 5.—E. R. 76893. Mycotic vulvitis limited to labia minora with leucoplakia-like area in interlabial fold.

The influence of ketone bodies has not been evaluated. In any event glucose alone did not cause tissue reaction, but in the presence of fungi it increased or induced distress. Certainly then, glucose may provide a more favorable medium, and thus may indirectly be the cause of the vulvitis. Nevertheless, the fungi as shown above are the responsible agents. Therefore, since the term, "diabetic vulvitis" is incorrect, it is suggested that "mycotic vulvitis" or "fungous vulvitis" be substituted.

of controlling the vaginal glycogen-like material in pregnancy remains undiscovered, and even such an alteration might predispose to other complications more serious.

BIOLOGIC ACTION

Perhaps the metabolic behavior of these yeastlike organisms may reveal an entirely different approach, or at least aid in a better understanding of this and similar disease processes.

The substance producing or mechanism resulting in irritation (pruritus primarily) and tissue reaction is unestablished.

Neuberg and his coworkers²³ have established some fermentation schemes of the yeasts on glucose. Their data show an oxido-reduction process, which appears to be simultaneous and continuous (Table VII). Tautomeric shifts are described also. Since they found 5 types of fermentation (Table VIII) one may anticipate others, especially in vivo.

TABLE VII. FERMENTATION SCHEMES

Type I—Neuberg	
(a)	$C_6H_{12}O_6 = 2H_2O + 2CH_2:C(OH) \cdot CHO$ (methylglyoxal)
(b)	$CH_2:C(OH) \cdot CHO + H_2 + H_2O = CH_2(OH) \cdot CH(OH) \cdot CH_2(OH)$ (glycerine)
	$CH_2:C(OH) \cdot CHO + O = CH_2:C(OH) \cdot COOH$ (pyruvic acid)
(c)	$CH_3 \cdot CO \cdot COOH = CO_2 + CH_3 \cdot CHO$ (acetaldehyde)
(d)	$CH_3 \cdot CO \cdot CHO + O = CH_3 \cdot CO \cdot COOH$ (pyruvic acid)
	$CH_3 \cdot CHO + H_2 = CH_3CH_2OH$ (ethyl alcohol)

TABLE VIII. FERMENTATION SCHEMES

Type II—Neuberg and Reinfurth	
$C_6H_{12}O_6$	$= CH_3 \cdot CHO + CO_2 + C_3H_8O_2$ (acetaldehyde) (glycerine)
Type III—Neuberg and Hirsch	
$2C_6H_{12}O_6 + H_2O$	$= 2C_2H_5O_3 + 2CO_2 + C_2H_5OH + CH_3 \cdot COOH$ (glycerine) (acetic acid)
Type IV—Neuberg and Kobel	
$C_6H_{12}O_6$	$= CH_3 \cdot CO \cdot COOH + CH_2OH \cdot CHOH \cdot CH_2OH$ (pyruvic acid) (glycerine)
Type V—Neuberg and Kobel	
$C_6H_{12}O_6$	$= 2H_2O + 2CH_3 \cdot CO \cdot COOH$ (pyruvic acid)

Nevertheless, some of those intermediary products may well be responsible, as acetaldehyde or pyruvic acid, for the symptoms and tissue reaction of vulvovaginal mycosis. In Type I fermentation, water and the enolic form of methylglyoxal are first produced from glucose. One molecule of methylglyoxal is reduced and hydrolyzed to glycerin while another is oxidized forming enolic pyruvic acid. After a shift to the

and potassium iodate a potent fungicide. The equation in Table V gives the chemical reaction. In vivo the vaginal acids are used to complete the reaction. To carry each mole of iodine freed, a mole of potassium iodide is necessary. Thus 8 moles instead of 5 of potassium iodide to one of potassium iodate is the correct ratio. By weight this is 6.2 to 1, and the theoretical yield is 49.3 per cent iodine liberated. Since this chemical reaction in solution is sudden, and iodine is prone to burn,

TABLE V. IODINE LIBERATED FOR VAGINAL FUNGICIDAL THERAPY

$KIO_3 + 5KI + 6HCl = 6KCl + 3H_2O + 3I_2$	
To keep Iodine in solution one mole of KI is added for each mole of Iodine liberated	
1KIO ₃ + 8KI yields theoretically 49.3% by weight I ₂	
Approximate molar weights and ratio per unit weight	
1KIO ₃ (214):8KI(1328)::1:6.2	
The vaginal acids are utilized to complete this reaction	

this mixture is diluted with neutral kaolin and dispensed in gelatin capsules. To guard against the premature liberation of iodine by acid impurities with the kaolin, this diluent is treated with ammonia and then dried to remove the excess. Capsules of 00 or 000 size contain approximately 0.125 gm. of the potassium iodide-potassium iodate mixture. The bulk of the content is kaolin. This allows for gradual solution and thus a gradual liberation of iodine over a longer period. Better results than with weekly or semiweekly application of gentian violet have been obtained by painting the vagina with diluted Lugol's solution (using the strongest concentration the patient can tolerate without discomfort, usually one-fourth strength) once a week, and the patient inserting 2 of these capsules in the vagina each night. Table VI indicates that generally patients can be cured within a period of several days or a few weeks. The results have been about the same for the pregnant and nonpregnant patient. The improved patients either discontinued therapy or delivered before completion of treatments.

The problem is not only to cure but to prevent re-infections. Further study is in progress along both of these lines. When and if patients receive treatment as Plass and others recommend,⁵ there is no particular

TABLE VI. RESULTS OF POTASSIUM IODATE—POTASSIUM IODIDE AS FUNGICIDAL AGENTS

NO.	PATIENTS TYPE	TREATMENTS		RESULTS
		NUMBER	AVERAGE	
20	Ob.	1-9	3.5	15 Cured 5 Relieved
8	Gyn.	2-6	3.4	7 Cured 1 Relieved

reason for another method. Our data so far do not reveal any particularly promising combined iodine preparation. Perhaps in vivo response may be somewhat different from in vitro. Satisfactory means

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DISCUSSION

DR. WILLARD R. COOKE, GALVESTON, TEXAS.—The determination of the importance of the cell-content of glycogen constitutes the most interesting and immediately practical phase of Dr. Hesseltine's work. There are four very commonly encountered conditions whose cardinal symptom is pruritus: trichomoniasis, the mycoses, senile and diabetic vaginitis. In each of these the mode of elimination of the causative factor differs widely, and some of the accepted modes of treatment of the one condition will make another worse. Trichomoniasis calls for treatment which brings about a low vaginal pH with an excess of glucose. Senile vaginitis is best treated with massive doses of estrin, which may create a high cell-content of glycogen. An excess of free glucose or of cell-glycogen creates an optimum condition for the growth of mycotic organisms. Hence it is necessary to make an accurate diagnosis before treatment is instituted.

In the case of mixed conditions, which are common, it is necessary to use good judgment in the choice and sequence of the therapeutic measures employed. We have found that it is best to eliminate the mycotic infection before proceeding to treat trichomoniasis with organic acid and glucose, or senile vaginitis with estrin. Fortunately, this is usually rather easy, through the use of gentian violet. Dr. Hesseltine's free-iodine treatment should be equally appropriate and represents a distinct advance in the management of persistent mycosis and the early stages of mixed conditions.

I am very glad to see that Dr. Hesseltine says that the exact identification of the mycotic organisms involved in a given case is unnecessary. Most doctors are rather inclined to "shy off" from the attempt to diagnose mycotic vaginitis, because they are under the impression that this requires an elaborate technical equipment. If the profession at large could be convinced of this mistaken idea, a great deal of unnecessary suffering could be eliminated.

Dr. Hesseltine's report of the relative frequency of mycotic infections in the pregnant, the nonpregnant, the premenstrual, and the adolescent groups, and in the pruritic and nonpruritic subgroups, coincide closely with our own observations. On the other hand, we have found mycotic vaginitis quite common in the immediate puerperium and in the pre- and postmenopausal groups.

DR. EVERETT D. PLASS, IOWA CITY, IA.—We have now accumulated sufficient data to cause us to eliminate that old name of diabetic pruritus vulvae and to utilize the etiologic nomenclature. It has been shown beyond question that the fungi can produce vulvitis and vaginitis, and in diabetic patients, the irritative symptoms are due not to the presence of glucose in the urine, but rather to the growth of the fungi in the sugar. In these diabetics with vulvar irritation, relief can usually be given in one of two ways. Almost immediate relief can be produced by application of one of the fungicides, or the same result can be obtained in the long run by treating the diabetes.

keto form, pyruvic acid yields carbon dioxide and acetaldehyde. A keto methylglyoxal and acetaldehyde are oxidized and reduced respectively into pyruvic acid and ethyl alcohol. Thus the process continues. Types 2, 3, 4, and 5 yield these products and acetic acid by other schemes.

Friedemann and Stenhouse²⁴ found that pathogenic monilia and cryptococci produced ethyl alcohol as readily as brewers' yeast. This observation suggests that the monilia and cryptococci may have a similar biologic action, but with a trend toward the production of particular intermediary or end-products which are responsible for the clinical entity. Since some features of certain stages of kraurosis and some types of mycotic vulvitis are similar, one may ask if there is not the possibility that in mycosis the precipitating factor is extrinsic and in kraurosis it is intrinsic.

CONCLUSIONS

1. Some of the recent contributions to monilial and cryptococcal vulvovaginal mycosis are reviewed.
2. A method requiring fewer office visits for treating vaginal mycosis is described.
3. It is emphasized that the term "diabetic vulvitis" is incorrect, since it is apparently a mycotic infection, and it is suggested that "mycotic vulvitis" or "fungous vulvitis" be used instead.
4. Glucose as such causes no irritation but produces a more favorable medium for the monilia and cryptococci.
5. Every patient with mycotic vulvitis should be examined for diabetes mellitus, and every diabetic patient with vulvar symptoms should be examined for mycotic infection.
6. The similarity of certain stages of mycotic vulvitis to kraurosis is mentioned.
7. Neuberg and coworkers' scheme illustrating mechanisms of fermentation of glucose by fungi is discussed in relation to biologic behavior. Such intermediary products as acetaldehyde or pyruvic acid may be responsible for the symptoms and tissue changes.
8. It is suggested that the fungi produce the precipitating factor extrinsically for the tissue reaction, while in such diseases as kraurosis it may possibly be intrinsically liberated.

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ANALGESIA AND ANESTHESIA AND THEIR BEARING UPON THE PROBLEM OF SHORTENED LABOR*

ARTHUR H. BILL, M.D., CLEVELAND, OHIO

IT IS very interesting to note the reaction of members of the medical profession toward the question of painless labor at various times during the last two or three decades. There was the period during which either nothing was given to relieve pain or merely a little chloroform as the head was being born and when in national obstetrical society meetings there was bitter opposition to proposals for relief of pain, all kinds of arguments, some quite silly, being made against such proposals. In years following, a continually increasing number of obstetricians had a more or less favorable attitude toward painless labor and instead of opposition there were efforts to develop new methods for relief. Many were suggested, perhaps in most cases too much stress being laid upon the individual procedure, even to the extent of making it a fad for the laity. Much that is disgusting has been published in lay journals. More recently we have heard renewed opposition to painless labor in medical circles. Bad results of childbirth have been attributed to analgesia and anesthesia, when in reality they were due to bad judgment or technique of poorly trained physicians. Unfortunately this has been quoted in lay journals, all to give the laity a very wrong impression of the real facts and values. Through all these years my associates and I have continued, unswayed by these discussions, to relieve all pain of labor and delivery, from start to finish, to the fullest extent of our ability to do so. Painless labor is not an experiment nor has it been considered such at the Cleveland Maternity Hospital during the last twenty or twenty-five years. From the results obtained in a very large number of cases we have no doubt as to the safety and effectiveness of our relief methods and have never had any hesitancy about continuing them but have rather been amazed at groundless arguments against such procedures.

It would seem that in spite of some unfavorable opinion the real question today is not whether to make labor painless but how to do this in the best way. The chief mistake of those who have advocated any particular method has been the attempt to make of it a means of conducting the entire labor painlessly. For example one may advocate morphine-seopolamine, cocaine ether, paraldehyde, the various barbiturates or avertin as if any one of these were a method in itself sufficient. No one

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We have continued using gentian violet because it is simple, is in itself nonirritating, and is generally effective. In the majority of our patients from one to three applications will give marked relief and sometimes effect a permanent cure. It is interesting, however, to know that in the more stubborn cases iodine preparations can be employed. We should bear in mind that there are available for vaginal insertion capsules which contain gentian violet. Hence even that form of therapy can be carried out by the patient independently.

The main problem in therapy for most patients is that of affording immediate relief and there is no question that gentian violet and the iodine preparations are effective in relieving irritation. The further problem of curing the patient completely is obviously difficult in some cases because of the possibility of reinfection. In the majority of our cases we have had no clue as to the mode of infection, and I am curious to know whether Dr. HesselDTine's recent studies have pointed in any way to the answer of that problem. In the wives of diabetic husbands, we sometimes find a very logical explanation for the mycotic infection of the wife since the husband may have a marked mycotic infection of the genital organs.

DR. ROBERT A. ROSS, DURHAM, N. C.—We have been impressed with the frequent findings of *Monilia albicans* unassociated with clinical manifestation. This led Jones to study the cultural and morphologic characteristics more closely, and he has established a new species which closely resembles *albicans* but does not give symptoms nearly so often. This strain has been named *Monilia stellatoides*. It varies from the *Monilia albicans* in five definite ways. It does not produce acid in saccharose. It is similar in other fermentation tests. On slide culture it rarely produces chlamydospores. On the blood agar plate the culture is star-shaped. When injected in the rabbit it does not cause death. It will not agglutinate in *Monilia albicans* serum.

Where there is any doubt as to the causative factor in vulvovaginitis, we resort to an intradermal test. Where the monilia is the causative factor, a local reaction will develop within a few hours and persist for as long as forty-eight hours.

In the more refractory patients, that is, those who have been treated over a long period of time by many different agents, we have employed vaccine therapy. Usually a definite reactivation of the process in the vulva occurs and persists until the patient is desensitized.

DR. ARTHUR H. CURTIS, CHICAGO, ILL.—I would like to ask if Dr. HesselDTine has used sulfanilamide in the treatment of this condition.

DR. HESSELDTINE (closing).—It is true, of course, that we do not have a safe and adequate way of controlling the glycogen content of the vaginal epithelium. Since this predisposing state cannot be avoided, curative and prophylactic means must be used.

As regards the possible sources of infection, Todd and others have found an 80 per cent frequency of fungi in the oral and intestinal tract. Thus a source through fecal contamination exists and is probable. Other patients may be carriers with the disease developing only when conditions are favorable.

I have not recommended the potassium iodide-potassium iodate mixture to replace gentian violet, so far it is recommended only for the patients that cannot be treated according to the ordinary method with gentian violet.

We have had no experience with sulfanilamide, the drug mentioned by Dr. Curtis. The mercurial, arsenical, and other compounds have been less efficacious fungicides. In vitro, at least, the element iodine possesses the greatest fungicidal potency.

and a half hours have already elapsed and the decision as to whether or not to give the dose is based merely on an estimation that not much more than one and a half hours additional will pass before the birth. The decision is commonly made with the aid of a rectal examination.

The scheme of dosage is as follows:

Morphine gr.	$\frac{1}{6}$	as soon as pains seem to hurt with no regard for the
Scopolamine gr.	$\frac{1}{150}$	amount of dilatation.
Scopolamine gr.	$\frac{1}{200}$	after forty-five minutes.
Scopolamine gr.	$\frac{1}{400}$	after another forty-five minutes and every hour and a half thereafter until discontinued.

As a rule, morphine is not repeated but in some cases, after several doses of scopolamine have been given, if the pains are unusually hard and the patient seems likely to feel them, an additional $\frac{1}{6}$ gr. is given. This is, however, in the exceptional case.

It is apparent that the observance of the three-hour rule makes scopolamine quite impracticable for use in cases of multiparas and as much as I regret this I have not felt safe in using it in such cases. The exception is the occasional case in which with slow dilatation and a rigid cervix we may decide, after watching, that the labor will simulate that of a primipara. In these cases a single dose is sometimes given to supplement the other method which is being used.

While nothing quite takes the place of scopolamine for primiparas, there is not such a striking difference between some of the better methods to be used for multiparas. I refer chiefly to sodium amytal, pentobarbital, ethyl ether and paraldehyde. I put them in this order, as in my opinion this is the way they should be rated. Sodium amytal is used at the Cleveland Maternity Hospital almost routinely as the medication for multiparas. There is very little difference between the action of sodium amytal and that of pentobarbital. Pentobarbital acts a little more quickly and wears off sooner. Therefore sodium amytal, the effect of which lasts longer, is to be preferred, for repetition of the dose will not as a rule be necessary. Sodium amytal also lends itself to combination with other sedatives far better. A maximum dose is not given. We do not vary the dose with the body weight but give 9 gr. at the beginning of labor. This would be an average dose and seems sufficient. It is given by mouth, but if an additional dose is necessary after several hours, it is given by rectum, usually being 6 gr. The effect ordinarily lasts at least three hours. In using sodium amytal in cases of multiparas, we do not fear fetal asphyxia and therefore, we do not observe the three-hour rule as in the use of scopolamine. We have no hesitation in giving sodium amytal before cesarean operations.

While results fairly comparable to those obtained from scopolamine are seen with sodium amytal, it cannot be said that there is as consist-

is entirely satisfactory. They should all be thought of as administrations to be given preliminary to analgesia by inhalation methods and general anesthesia. They are only suitable for the first stage of labor. The latter part of labor is conducted in a far better way with inhalation anesthesia. In other words late in labor the degree of amnesia or anesthesia should be under the complete control of the anesthetist who can at will deepen or lighten the anesthesia according to the demands of the individual case and not be handicapped by the action of a drug which may produce deep hypnosis and will only be eliminated after a lapse of time. If the action of the drug which has been given to cause amnesia has practically or entirely worn off by the time of delivery there is a distinct advantage. The importance of this varies with the drug used being greater, perhaps, in the case of morphine-scopolamine than in the others but applies somewhat to all. The basis of our routine practice is, therefore, to consider medication as essentially suitable for the first stage or a little less and the general anesthetics for the second stage and latter part of the first stage.

There is much difference of opinion as to the relative merits of different forms of medication. In contrast to cases in which no relief is offered they are all good. However, after trying most of them, experience has given me more confidence in some than in others and our procedures are based upon this experience. I cannot find any method of premedication which is so uniformly satisfactory in cases of primiparas as morphine and scopolamine. In it I have found a method which does not interfere with the progress of labor and as we use it, is safe for mother and baby and very consistently leaves with the patient little or no recollection of the entire labor. The completeness of its action in this respect is not equalled by other medication. Criticism of scopolamine as a cause of fetal mortality is undoubtedly due to the manner in which it is used. I refer especially to attempts to make of it a method for conducting the entire labor and giving it in the second stage and in the most uncertain labors of multiparas. If this is done the babies will, in a certain number of cases, be in a state of serious apnea. Realizing its limitation in this respect we have adhered to a definite rule, that scopolamine should not be given within at least three hours of the expected time of birth. The observance of this rule has probably, to a very large extent been responsible for our uniformly good results from the use of scopolamine in more than 20,000 cases. When the three-hour rule is observed, the baby shows no serious apnea. We very frankly do not believe that we have lost any babies as the result of this procedure. It is seldom difficult to time the administration to conform to this rule. For example after the first three hypodermies, which are given forty-five minutes apart, $\frac{1}{400}$ gr. of scopolamine is given hypodermically every one and a half hours until discontinued. When the next dose is due, one

As previously stated one should not depend upon medication entirely for the relief of pain. As the pains become harder, it is better to supplement this by inhalations of a general anesthetic given at first merely during the uterine contractions as analgesia, later on continued lightly between contractions and eventually deepened to anesthesia for the delivery. Clever administration of the general anesthetic is really the most important part of the conduct of painless labor. However, inhalation analgesia alone is not entirely satisfactory without the basic medication which tides over the interval between pains and has a decided quieting effect on the patient and does away with the disagreeable sensation of repeatedly going under and coming out of the anesthetic. The result of the combination is an unbroken period of amnesia. As the medication wears off later in labor, it is important that enough anesthetic be given to prevent the patient from at any time becoming conscious of what is going on and thus preventing any break in the continuity of the treatment. To give just enough anesthetic to relieve pain and not slow the labor is a real art, but is accomplished in a remarkable manner by an anesthetist also trained in obstetrics who has an understanding of the greatly varying action of the uterus in different labors and of the emergencies which may arise. We believe that the ideal anesthetist is the nurse anesthetist who has previously had responsibility in obstetric surgery.

The administration of ether for analgesia and only during contractions should be given with a closed cone so that a sufficient amount may be given in the shortest time. Drop methods are altogether too slow for this purpose. Much of the success also depends upon the alertness of the anesthetist in anticipating the pains. This is accomplished by keeping a hand on the patient's abdomen and applying the anesthetic as soon as the uterus begins to contract, which is usually before the patient shows any other evidences of the onset of pain. If the anesthetic is applied only after the patient complains of pain, it is too late to give satisfactory relief.

The proper choice of the anesthetic to be used in each case is important. From a strictly obstetric point of view, we may divide anesthetics into two classes, first, those which tend to cause relaxation of the uterus, and second, those which are relatively nonrelaxing. Both kinds should be available for use during labor. Ether is a good example of the first, while nitrous oxide and oxygen represent the second. We consider these the most satisfactory from the standpoint of safety and effectiveness. Tracings showed that when ether is given only for analgesia there is no appreciable effect on the uterine contractions. However, if ether is given to the point of surgical anesthesia, it is possible to stop the contractions entirely. Nitrous oxide caused no diminution of uterine contractions when used for analgesia, and even when the patient was under deep anesthesia, it was not possible to cause complete relaxation.

ently the same complete obliteration of the consciousness of the entire labor. In this respect we have, however, found it to be a method which gives more uniformly satisfactory results than either paraldehyde or colonic ether.

The effect of these various drugs upon the progress of labor as shown by tracings of uterine contractions was studied by Dodek and later by Moore while on my service at the Cleveland Maternity Hospital. Following is a brief summary on their findings.

In established labor scopolamine has no appreciable effect upon the uterine contractions. The initial dose which is combined with morphine will probably give a morphine action which is a moderate depression in the intensity of a few contractions. The action of morphine is quite variable, clinical experience being that it sometimes hastens dilatation. The slight and temporary effect is over by the time the next dose is given and the contractions become as strong as before and remain so while scopolamine alone is given in the subsequent doses.

Sodium amytal does not diminish the force of uterine contractions nor interfere with complete relaxation between them. Dilatation progresses very normally.

Colonic ether has very little effect upon the uterine contractions when combined with quinine. We use it supplementary to morphine and scopolamine or sodium amytal in some of the more prolonged labors in which, without it, inhalation anesthesia would be necessary over an impractical length of time. It is not often used as a primary medication and is limited to the first stage of labor.

The effect of paraldehyde is a temporary diminution of the intensity and duration of uterine contractions; however, this effect is usually quite brief, the contractions regaining their previous character within a half hour. Its sedative effect is quite variable in different patients.

The effect of avertin is a prolongation of the intervals between the contractions. Furthermore, its analgesic effect is of too short duration to make it worthy of serious consideration.

Comparing the effects of the first four, morphine and scopolamine, sodium amytal, colonic ether and paraldehyde, we cannot say that with any one of them there was enough interference with uterine contractions to make it unsuitable as an analgesic. Our selection of one in preference to another is therefore based largely on the consistency and completeness of its action in causing amnesia and analgesia.

Scopolamine and sodium amytal constitute the basic medication which we use for preliminary analgesia and are in themselves sufficient for this purpose in the average case. However, we use many combinations in the more difficult cases, according to their demands, and do not adhere strictly to the original method if the patient does not seem to be entirely relieved of pain.

Many of the nervous symptoms of pregnancy, including nausea and vomiting, have undoubtedly been due to or aggravated by a dread of an event which the patient has been taught from girlhood to think of as a terrible ordeal. In a community in which the patient knows that she will not suffer during her labor, much of this is eliminated and her mental state is greatly improved. However, the outstanding advantage is seen in the control of the latter part of the labor and delivery by the anesthetist, who can by the proper selection of the anesthetic and the careful regulation of the amount administered control at will the force of the uterine contractions. The following typical cases illustrate the advantage of being always ready to diminish the force of or completely stop the contraction without delay when the baby shows signs of distress due to pressure. There is the occasional case in which, due to unusually forcible pains, the fetal heart becomes alarmingly slow, at first during a contraction and then continuously. Deeper anesthesia with ether will usually cause the fetal heart to return to normal by taking excessive pressure off the baby. I have seen some very striking examples of this kind in which there can be no doubt that the skillful administration of ether saved the baby's life. In such a case the fetal heart is counted constantly and the amount of ether given is regulated according to the heart rate. Fear of harm to the child from the anesthetic is all too common and unfounded. In most cases of fetal distress there is actual benefit from the administration of more anesthetic. This should, however, be of the more relaxing type (ether), and if it happens that nitrous oxide is being given at the time, change should be made to ether. In other words, fetal distress sometimes attributed to the anesthetic is on the contrary, invariably, due to the labor. Also consider the case in which, during hard second stage pains, there is an increased amount of bleeding accompanied by a variability of the fetal heart. The diagnosis is plain. The placenta is beginning to separate and there may be complete separation with the death of the fetus if contractions continue. The uterus should be immediately put to rest by complete surgical anesthesia and delivery accomplished. Other examples are the prolapsed cord and beginning contraction ring. In all of the cases in this group a relaxing anesthetic (ether) must be used. Nitrous oxide will not do.

The way in which the anesthetic is of great value to the obstetrician is well illustrated by our usual procedure in a forceps delivery. Contractions are allowed to go on until it is time to deliver. The patient is then relaxed for the local preparation, the ironing out of the perineum and for any necessary manipulation such as rotation of a head from a posterior position. The anesthetic is then decreased so that contractions will increase during the descent of the head. We lay great stress on this and make traction with forceps only during a uterine contraction.

If there are no other indications or contraindications, the choice of anesthetic is made with this action in mind so as to adapt it to the individual case. For example if the pains are very strong and frequent or perhaps too strong, ether is given. If the pains are not very effectual and infrequent, nitrous oxide and oxygen is preferable.

Relief for pain is given to each patient as soon as she seems to suffer, with no regard to the amount of dilatation. As a rule it is not necessary for her to ask for analgesia for her wishes are anticipated. However, a patient who asks for relief is never told that she "must wait," that it is "not time to give anything" or that "the pains are not hard enough." We believe that the patient is the best judge of her sense of pain. A patient admitted to the hospital in hard labor is relieved by the quickest method which is inhalation. In some cases, chiefly primiparas, this is only temporary and may be discontinued for a varying period after the first stage medication becomes effective.

The following summary illustrates the average number of hours during which inhalation analgesia and anesthesia are used.

Inhalation analgesia and anesthesia as administered to 100 consecutive patients in labor, consisting of 25 private and 25 staff primiparas and 25 private and 25 staff multiparas.

PRIMIPARAS

Analgesia:

Nitrous oxide-oxygen	Ether
13 cases	37 cases
Average duration per case	Average duration per case
2 hours and 5 minutes	2 hours and 52 minutes

Anesthesia:

Nitrous oxide-oxygen	Nitrous oxide-oxygen-ether	Ether
2 cases	10 cases	38 cases
Average 33 minutes per case.	Average 50 minutes per case.	Average 38 minutes per case.

Average duration of labors 15 hours and 24 minutes

Average duration of inhalation analgesia and anesthesia per patient 3 hours and 18 minutes.

MULTIPARAS

Analgesia:

Nitrous oxide-oxygen	Ether
15 cases	35 cases
Average duration per case	Average duration per case
1 hour and 4 minutes	1 hour and 48 minutes

Anesthesia:

Nitrous oxide-oxygen	Nitrous oxide-oxygen-ether	Ether
2 cases	14 cases	34 cases
Average 43 minutes per case.	Average 37 minutes per case.	Average 27 minutes per case.

Average duration of labor 9 hours and 30 minutes.

Average duration of inhalation analgesia and anesthesia per patient 2 hours and 15 minutes.

We have seen benefits from the use of analgesia and anesthesia in labor considerably broader than the mere relief of pain. The convalescence of the patient is smoother and less accompanied by nervousness.

birth or operative delivery depends more upon the judgment of the obstetrician than upon the anesthesia. I personally prefer to correct abnormalities of position such as occipitoposterior and deliver. When the head is in an anterior position, it is my custom to let it descend to the perineum, which it will do in a large percentage of cases, and then deliver by low or prophylactic forceps. I prefer to use prophylactic forceps not because the anesthetic makes it necessary, but because I believe that there are distinct advantages, including a better aseptic technique, more skillful control of the rapidity of the birth, and prevention of unnecessary prolonged pressure upon the child's head.

Something should be said about the often mentioned danger of anoxemia. Some examinations of both maternal and fetal blood at the time of delivery have been made by Dr. J. W. Mull at the Cleveland Maternity Hospital. They show that there is no anoxemia after ether anesthesia. In the use of nitrous oxide-oxygen anesthesia Eastman found that a mixture of 90-10 caused anoxemia which was serious for the baby while one of 85-15 caused no serious anoxemia. In our service this anesthetic is not given in a mixture less in oxygen than 80-20 which seems perfectly safe for the baby.

Danger of anesthetics contributing to postpartum hemorrhage, by causing too much relaxation of the uterus, may be avoided by medication. It is our routine practice for this purpose to give 1 c.c. of pituitary preparation as soon as the baby is born and an ampule of ergotrate, intramuscularly, as soon as the placenta is delivered.

There is a small group of cases, chiefly those with infection of the respiratory tract, in which the general anesthetics must be used with great caution or avoided. In these cases ether is avoided in any event and if the case is such as to forbid the use of nitrous oxide, as well, the usual medication may be followed by perineal nerve block with novocaine, the results being fairly satisfactory, though, of course, not at all comparable to those obtained from the use of general anesthetics.

Naturally it must be assumed that for conducting the type of labor here described there must be adequate facilities, usually found only in hospitals.

The summary which follows will illustrate results which may be obtained from the treatment herein described. It is a summary of the last 240 consecutive occipitoposterior cases which I have personally delivered from the time of a previous publication up to date. It would seem that occipitoposterior cases would serve well for purpose of illustration, because they are probably the most troublesome of all. In this series all of the patients were given analgesia and anesthesia both by medication and inhalation and the deliveries were all operative, being either rotation of the head by forceps followed by forceps delivery, or internal podalic version. The way in which varied combinations of medication are used is illustrated.

The anesthetist keeps a hand on the patient's abdomen and announces the onset of each contraction. Simultaneously traction with forceps is then made. In this way the amount of pull needed is reduced at least 50 per cent. The amount of traction used in forceps delivery was studied by Dr. Burdette Wylie with the use of a "tractionometer." The average pull in cases of primiparas was 13.7 kg. and in cases of multiparas 10.03 kg. In the latter, however, there were many in which the pull was less than 5 kg. The figures correspond very closely to the estimated force of the uterine contractions. Therefore, without the aid of the contractions twice as much traction would be necessary. When the head is crowning, the anesthesia is deepened to the point of relaxation for the actual delivery and is then either discontinued temporarily or lightened for the third stage to again encourage contractions. For any necessary repair following delivery of the placenta there is ordinary continuous anesthesia.

Anesthesia given in the way described is not easy for the anesthetist, being much more complicated than that for the ordinary surgical operation, but contributes very greatly to the results, especially in the more difficult cases.

For this type of delivery nitrous oxide-oxygen is preferable to ether because of its lesser tendency to relax the uterus. However, even under light ether anesthesia contractions sufficient to enhance the traction force are seen. On the contrary in cases in which internal podalic version is to be performed, the use of nitrous oxide-oxygen is contraindicated, for the uterus is quite likely to contract during the version and make it a dangerous procedure. For such cases we use ether anesthesia.

Painless labor and shortened labor are sometimes discussed as if the latter were a natural sequence of the former. Undoubtedly those who speak of shortened labor are thinking of meddling and harmful interference. To analyse this question we must rightfully consider the first stage and the second stage separately. There can be no doubt that much of the bad obstetrics is due to attempts to terminate the labor before the cervix is fully dilated. The longer one practices obstetrics the more he respects the resistance of the cervix. In my opinion the cervix has been the cause of more stillbirths than has the bony pelvis. Attempts to deliver the baby before full dilatation except in most urgent cases constitute meddling interference. Probably one of the chief reasons why a doctor does this is to terminate the suffering of the patient, especially when influenced by the demands of the family to "do something." If the patient is not suffering there are usually no such demands and the physician is free to let the first stage run its course. It would seem that instead of relief of pain leading to this type of interference it is the surest way of avoiding it. The same principle could apply to the second stage, for whether there is spontaneous

longer tell of the harrowing details of labor to frighten their expectant friends. And the patient who has had one baby with little pain stands in no great fear of the next labor.

Another and unexpected advantage has been an apparent shortening of the first stage of labor. While we can never say what would have happened without analgesia in a given case, yet the more rapid progress after giving analgesia is so often noted that it does seem more than a coincidence.

One must, however, face the fact that the giving of pain-relieving drugs creates new problems. The lack of coordination of the patient under the influence of pain-relieving drugs often causes a slowing down of the progress of the second stage of labor. This results in an increased incidence of interference. Furthermore, a restlessness often develops which may cause one to despair of being able to conduct the delivery in an orderly and aseptic manner. About the only solution of this problem is an anesthetic and an operative termination of labor. This may present no new problem for the obstetrician who delivers all patients by operative means after the first stage of labor is ended, but to those who like to allow their patients to deliver spontaneously, it means a definite change in procedure. We cannot believe, as Dr. Bill states, that this is entirely a choice of the obstetrician. We do agree with the essayist that with the use of pain-relieving drugs one can be freer to wait until interference is of the minor type.

Furthermore, there are certain special dangers and special management and selection are necessary to avoid these. Irving has called attention to the fact that pneumonia is a possible complication if the patient has an upper respiratory infection, which is in accord with our experience. The lessening of reflexes also makes aspiration of vomitus a danger. Prolonged labors may be accompanied by a dehydration which may require active treatment.

In general, we have felt that pain-relieving drugs had no untoward effect on the babies. It is true that the babies are often listless and require definitely more resuscitation to establish respiration and a healthy, vigorous cry.

Our complacency in this matter was somewhat shaken recently by the work of Schreiber of Detroit. Schreiber bases his opinions on Courville's brain findings in cases of death following nitrous oxide anesthesia, and on his own findings in cases of death due to industrial gases. In cases with cyanosis an anoxemia may cause a focal necrosis of brain cells, which if not fatal will later result in spastic muscles or in mental deficiencies. Schreiber bases his assumptions in regard to analgesia on a series of babies with spastic muscles, which he believes have had brain cell necrosis caused by cyanosis. While Schreiber's work is not conclusive and not entirely convincing, he has pointed out the existence of a possible danger where we thought none existed. His work has caused us at Harper Hospital to give more careful consideration to dosage.

We are not in accord with Dr. Bill that the aim should be to have a completely painless labor. We believe the labor should be allowed to progress for some time and that the drug should be given only when the pain becomes definitely annoying. We also feel that our patients need not be kept so deeply under the influence of the drug as was at first our practice. With a smaller dosage the patients may complain of distress, but be completely forgetful of it after the labor is over.

In general, we feel that to conduct labors safely with analgesia requires the best of hospital facilities. The new problems created tax the resources of even the better trained obstetricians. The greatest danger is that many of these procedures may be practiced by men who have not the facilities or the skill to meet all the problems. When we advocate something that is safe in expert hands, we must not forget that the general practitioner is still the obstetrician for the masses. In less skilled hands the pain-relieving drugs may add to maternal mortality and morbidity.

OCCIPITOPOSTERIOR		AVERAGE DURATION OF LABOR	
Primiparas	119	First Stage:	
Multiparas	121	Primiparas	17.79 hr.
		Multiparas	8.69 hr.
Total	240		
Vertex L.O.P.	109	Second Stage:	
Vertex R.O.P.	131	58 minutes	
MEMBRANES RUPTURED		METHODS OF DELIVERY	
Before onset of labor	28	Internal podalic version	125
At onset of labor	9	Foreeps rotation and delivery	115
During first stage	72	High medium	9
During second stage and at delivery	112	Medium	56
Questionable	19	Low or low med.	50
		Voorhees' bag	6
		Episiotomy	89
ANALGESIA PRIMIPARAS		ANALGESIA MULTIPARAS	
Morphine and Scopolamine		Sodium Amytal	
Plus ether	48	Plus ether	56
Plus colonic ether and ether	12	Plus nitrous oxide	37
Plus sodium amytal, colonic ether and ether	4	Plus colonic ether and ether	8
Plus sodium amytal and ether	5	Plus colonic ether and nitrous oxide	2
Plus nitrous oxide	41	Varied	2
Plus colonic ether and nitrous oxide	2	Inhalation ether	13
Varied	5	Nitrous oxide and ether	5
ANESTHESIA FOR DELIVERY		MORTALITY	
Ether	149	Maternal	0
Nitrous oxide	7	Fetal corrected	0
Nitrous oxide and ether	84	2 died; both had congenital malformations incompatible with life	
Total	240		
MORBIDITY		MORBIDITY	
After first 24 hours postpartum, temp. 38° or over for two successive days—temp. not necessarily continuous.		1 Acute "cold"—Temperature on admission and 3 days	
13 cases—5.4%		1 Mastitis. Temperature on 12th and 13th days	
		5 Pyelitis	
		1 Tonsillitis	
		5 Cause uncertain. Temp. of 38° on only two occasions. Normal afterward	

From the results obtained in this series, it must be apparent that the medication and anesthesia had no deleterious effect upon either mother or child. On the contrary it would seem that the clever administration of anesthesia has contributed in no small way to the saving of babies' lives in a fair number of cases.

2105 ADELBERT ROAD

DISCUSSION

DR. GEORGE KAMPERMAN, DETROIT, MICH. (by invitation).—In general the application of pain-relieving drugs in obstetrics has been a definite advance, but a final solution has not yet been reached. The aim of these methods in obstetrics has been to relieve or diminish the pain of labor, and this aim has been accomplished to a great extent. This has had a favorable psychic effect on the patients, and they no

inevitably some type of operative delivery follows. I feel, therefore, that this Society should give some note of warning against a routine method of trying to produce painless childbirth.

DR. COLLIN FOULKROD, PHILADELPHIA, PA.—Any procedure reported from this Society is going to be applied by the great majority of men who have graduated within the past five years. It is very unwise to allow those men without experience to use these drugs, on the word of a man, who has had 2,000 or more cases, that he can conduct labor successfully with them.

Women often insist upon amnesia, but we should sift out the patients who can be properly treated in this way. The doctor must, however, carry her through with the least possible damage to herself and the baby. Amnesia certainly reduces the mental control which is needed in the latter half of labor. Following this method universally will lead to disaster.

A personal selection of the drug is essential. Some women become excited. Some will immediately relax the cervix by the use of sodium amytal, while in others it will have no effect on the cervix. Long before this method was instituted Dr. Newell read a paper which embodied the same ideas and which some of us still carry out, but based upon morphine and scopolamine.

If you will encourage your patients to go on to two fingers dilatation you will have them come through the labor without any serious remembrance of the difficulties of labor in normal cases. There is no question that sodium amytal is beneficial in many deliveries. I merely suggest that patients should be classified, and that if they want analgesia they should go to a skilled obstetrician and not to a general practitioner.

DR. HARVEY B. MATTHEWS, BROOKLYN, N. Y.—In 1915 when Dr. John Polak came back from the Krönig and Gaus Clinic in Germany, he brought with him the technique of "Dämmersehlaf" or "twilight sleep," i.e., morphine and scopolamine analgesia and amnesia. From an experience extending over these twenty years, it is still the analgesic of choice so far as I am concerned. Furthermore morphine-scopolamine is the safest drug for the general practitioner to use.

Cyclopropane anesthesia is to be recommended for your serious consideration. It requires 80 to 90 per cent of oxygen to be given with it, and therefore with this amount of oxygen the baby is never asphyxiated.

In all of these methods under discussion, the man who is giving the analgesia after all holds the balance of success or failure in his hands. If he has had enough experience and his judgment is sufficiently sound he can take any of these drugs and produce satisfactory results with them.

DR. CARL H. DAVIS, WILMINGTON, DEL.—Various clinics have developed plans for pain-relief which work for the average patient. Most of us will agree, however, that the obstetrician should be familiar with all methods and adapt the procedure to the problems presented by the individual patient rather than attempt to adapt the patient to a particular method of pain-relief.

The general plan which I have employed for a great many years has been to use hyoseine and heroin for the first stage of labor and nitrous oxide analgesia for the second stage. This is satisfactory for the majority of patients. Occasionally I have used rectal ether because I wished to secure a slowing up of labor over a considerable period of time for a patient who had a slowly dilating type of cervix. During the last few years I have used barbiturates somewhat as a first stage procedure. The woman who comes to the hospital with beginning but not active labor, will have sufficient discomfort to keep her from sleeping. A dose of 6 gr. of sodium amytal will be sufficient to give that woman a few hours of satisfactory rest. I follow this with heroin and hyoseine analgesia in the first stage of labor, and then give intermittently a nonexplosive type of inhalation gas in the second stage.

DR. G. D. ROYSTON, St. Louis, Mo.—In the last 20,000 deliveries in the Washington University Clinic, a majority of the patients have received scopolamine or hyoscine in various combinations. The substitution of barbiturates for opiates has broadened the scope of its use and given increased satisfaction.

We agree with Dr. Bill's indications for painless labor, feeling that much premature interference is avoided, when the obstetrician is spared the importunities of the patient. We disagree with him in limiting hyoscine to primiparas. In our clinic, whenever we consider the patient is definitely in labor and complaining of pain, regardless of parity, analgesia in some form is administered. Ward patients must have $2\frac{1}{2}$ to 3 fingers dilatation before receiving hyoscine. During the prodromal stages, often barbiturates alone are given. Ordinarily hyoscine in ampule form is injected with $\frac{1}{6}$ gr. or less of morphine sulphate. Barbiturates may be substituted for opiates. The desired degree of semimarcosis is maintained by repeated doses of hyoscine, properly spaced, and is determined by the patient's locomotor coordination, dilatation of pupils, etc. This is continued until delivery actually occurs. The method of delivery is more optional with the obstetrician than a matter of necessity. The opiate, if any, is never repeated after the initial dose.

Animal and clinical studies convince us that fetal respiratory difficulties may follow the administration of opiates given late in labor. Hyoscine in the doses used has little or no effect on respiration. The effects produced on respiration by morphine are twofold, the one directly on the respiratory center, the other on the constricting muscles of the bronchiole.

We disapprove of inhalation anesthetics during the first stage of labor, except for the occasional case, and we limit nitrous oxide to the late second stage of labor. Ether or chloroform on the open mask is used during the actual delivery when there are no contraindications from the cardiac, pulmonary, or toxemic point of view. Ether is regularly used for repair. An interne and a nurse remain constantly with every patient under semimarcosis. Probably 10 per cent to 20 per cent of such patients are restless and require restraint, yet have perfect amnesia. This restlessness and the need of constant attendance of trained help are the only disadvantages of the method as we use it.

We feel that morphine-hyoscine modified with barbiturates is the most valuable method of semimarcosis available. It can be safely and profitably used by any one who thoroughly understands the action of these drugs. The earlier reports which have stressed increased fetal asphyxia have been chiefly due to improper use of the method and too much general anesthetic at the time of delivery. Fetal asphyxia occurs without analgesic methods and the increased asphyxia that results from such methods is minimal, it having no effect upon fetal mortality as our reports in the past have repeatedly shown.

DR. WILLIAM A. SCOTT, TORONTO, CANADA.—The alleviation of pain in the first stage of labor is one thing, the routine attempt to produce painless childbirth is another. It is undoubtedly true that the skilled obstetrician working with a skilled anesthetist, under the most perfect circumstances and surroundings, can without any great difficulty and with a high degree of success get painless childbirth. It is to be remembered, however, that if he does this, and more particularly if he teaches it, the general practitioner without his skill and without ideal surroundings will be forced to attempt the same procedure.

I know no method of painless childbirth that does not in a fair percentage of cases lead to great restlessness. With unfavorable surroundings one of two things must follow, either complete anesthetization of the patient and instrumental delivery, or else a deepening of that drug narcosis which we know is not free from danger. More than that, one finds that if the obstetrician, who is anxious to succeed in producing a painless labor, finds that his method is not going smoothly, then

dilatation, that there were no deaths. Labor was allowed to progress without interference. If bleeding occurred before the onset of labor, contractions were induced in some instances by rupture of the membranes or by metureurysis. Of the total 204 cases delivered through the pelvis, 5 or 2.4 per cent received transfusions, as did an equal number, or 16.7 per cent of the 30 cesarean sections. The increased frequency of transfusion among the cesarean sections indicates a greater blood loss than was the case with those women delivered through the pelvis.

TABLE I. THE RÔLE OF INTERNAL HEMORRHAGE AND TOXEMIA IN DETERMINING MORTALITY

	CASES	DEATHS	PER CENT MORTALITY
No toxemia	224	8	3.5
Toxemia	129	10	7.7
External hemorrhage	234	4	1.7
Internal hemorrhage	119	14	11.8

TABLE II. EXTERNAL HEMORRHAGE. BOSTON LYING-IN HOSPITAL. MATERNAL MORTALITY ACCORDING TO THE METHOD OF DELIVERY

	CASES	DEATHS	PER CENT MORTALITY
Normal delivery, low forceps, breech	170	0	0.0
Pelvic operative delivery	34	3	8.8
Cesarean section	30	1	3.3

TABLE III. EXTERNAL HEMORRHAGE. FETAL MORTALITY

	PELVIC DELIVERY 207 INFANTS (INCLUDING 3 PAIRS OF TWINS)		CESAREAN SECTION 30 INFANTS	
	NO.	P.C.	NO.	P.C.
1. Dead on admission	29	14.0	5	16.7
2. Under 4 pounds	32	15.4	6	20.0
3. Stillborn	45	21.2	7	23.3
4. Died after birth	27	13.0	4	13.3
5. Gross mortality (3) + (4)	72	34.7	11	36.7
6. Not dead on admission or under 4 pounds	146		19	
7. Net fetal mortality (6)	11	7.5	0	00.0

Of the 237 infants in this group, including 3 pairs of twins, 34 or 14.3 per cent were dead *in utero* when their mothers were admitted to the hospital. Moreover, 40 others, or 16.8 per cent, although alive *in utero*, were under 4 pounds in weight when born. In almost one-third of the cases, therefore, salvage of the infants was either impossible or unlikely. In assigning proper values in fetal mortality to methods of treatment, the net death rate, which applies only to those infants alive on admission and over 4 pounds, is of more importance than the gross death rate, which embraces all infants, regardless of their vital condition or size.

DR. GEORGE W. KOSMAK, NEW YORK, N. Y.—The combination of morphine and atropine is a tried and old combination. 'The atropine undoubtedly enhances the effect of the morphine and in the rigid cervix has a remarkable effect in relaxing it. Dr. Davis' mention of heroin is of interest. To most of us that drug is unavailable for it is banned in New York State.

DR. BILL (closing).—I wish further to emphasize the point that we must not adhere to any one method but rather use a combination of several methods adapted for the individual patient. We must consider the safety of the baby primarily. In the series of cases reported which had no fetal mortality (corrected) the analgesia evidently had no ill effects. Blood studies of cases in which gas and ether anesthesia were used showed no anoxemia. In starting the analgesia we do not wait for 2 or 3 fingers dilatation but give medication or inhalation analgesia as soon as the patient complains of pain.

In comment upon the argument that such procedures as these are not safe in the hands of the general practitioner, I think that we must stop lowering our standards to the level of the untrained man and must begin to think of training men to do the things which we consider ideal.

THE CONSERVATIVE TREATMENT OF PREMATURE SEPARATION OF THE NORMALLY IMPLANTED PLACENTA*

FREDERICK C. IRVING, M.D., BOSTON, MASS.

(From the Department of Obstetrics, Harvard Medical School, and the Boston Lying-In Hospital)

THE maternal death rate in premature separation of the normally implanted placenta is increased if the hemorrhage is internal; that is, retained within the uterine cavity, or if there coexists a toxie state, such as preeclampsia, eclampsia, or nephritis. From Jan. 1, 1916 to April 1, 1937, 353 patients with premature separation were admitted to the Boston Lying-in Hospital, all beyond twenty-eight weeks of pregnancy. Table I shows the relative distribution of deaths depending upon these two factors. It is evident that retention of blood within the uterus was more often associated with a fatal outcome than was the presence of toxemia. Therefore these 353 cases are divided into two groups: those with external hemorrhage and those with internal hemorrhage.

EXTERNAL HEMORRHAGE

There were 234 cases in this group. Since this report concerns only methods of treatment and their results, no other aspects of premature separation will be considered. In Table II are given the maternal mortalities following simple pelvic delivery, complicated pelvic delivery, and cesarean section. One notes in the 170 patients delivered normally, by low forceps or by the breech, in every instance only after full cervical

*Read at the Sixty-Second Annual Meeting of the American Gynecological Society, held at Swampscott, Mass., May 31 to June 2, 1937.

TABLE V. INTERNAL HEMORRHAGE. RESULTS WITH CESAREAN SECTION AS REPORTED BY VARIOUS AUTHORS

AUTHOR	CASES	DIED	PER CENT
Willson ¹	21	4	19.0
Brodhead ²	8	3	37.4
Williams ³	10	3	30.0
Fitzgibbon ⁴	4	1	25.0
Davis and McGie ⁵	29	4	13.8
Siegel ⁶	11	2	18.2
	83	17	20.5

indeed there is no other fairly frequent complication of pregnancy, with the possible exception of eclampsia, that has been so often fatal. The woman with this form of internal hemorrhage is not only handicapped by acute blood loss, but she is also often the victim of shock caused by sudden distention of the uterus. In three-fifths of the cases toxemia is present, on occasions accompanied by partial or complete suppression of urine. It would be difficult to envisage a more dangerous basis for such a surgical operation as cesarean section, a procedure in itself of considerable magnitude and often complicated by further hemorrhage. All judgment should be against it, provided there exists a safer and less radical means of escape.

Such a solution of the difficulty was brought to the attention of American obstetricians in 1931 by the late John Osborn Polak.⁷ He reported 16 cases of internal hemorrhage treated by rupture of the membranes, the insertion of a tight cervical and vaginal pack and the application of a Spanish windlass abdominal binder. This treatment was based upon the method in use at the Rotunda Hospital in Dublin. Only one of Polak's patients died, giving a mortality of 6.2 per cent. Discouraged by our results with cesarean section in these cases at the Boston Lying-In Hospital, we began the use of Polak's method, and in 1934 I reported before the New York Obstetrical Society an equal number of cases, also with one death, and thus accompanied by the same mortality. In 1936, Heffernan⁸ of Boston recorded 7 cases with no deaths.

It has been stated that since the uterus is often infiltrated with blood and serum it is paralyzed, and therefore it cannot expel its contents. In only one case in our series of 34 patients treated conservatively did this occur; the remaining 33 delivered themselves normally or by low forceps. The only fatality occurred in this woman who entered with jaundice, a severe toxemia and suppression of urine, and died undelivered. It is beyond probability that cesarean section would have saved her life. Fear has also been expressed, for the same reason, that the uterus would fail to contract following delivery, and that the patient would succumb to postpartum hemorrhage. Our experience has been that the uterus has behaved well. In only one instance was it necessary to resort to tamponade. The most remarkable argument advanced by

Among the infants delivered through the pelvis the net fetal mortality was 7.5 per cent, while with cesarean section it was zero. The gross mortality in both instances was about the same being 34.7 per cent in pelvic delivery and 36.7 per cent in cesarean section (Table III).

INTERNAL HEMORRHAGE

In this class are all cases where the bulk of the hemorrhage was retained within the uterus. Bleeding which is entirely concealed is the exception, since in all but 2 of our 119 cases of internal hemorrhage, there was some visible bleeding at some time. Internal hemorrhage has also been described as *ablatio placentae* or *abruptio placentae* according to which appellation most suits the fancy. This type of case is often accompanied by the so-called uteroplacental apoplexy, although unless one inspects the uterus either at operation or at autopsy, no one may know which patients present this anatomic picture and which do not, since there are no characteristic physical signs denoting the infiltration of the myometrium with blood and serum.

TABLE IV. INTERNAL HEMORRHAGE. FETAL MORTALITY

	PELVIC OPERATIVE DELIVERY 16 INFANTS		CESAREAN SEC- TION 70 INFANTS (1 PAIR TWINS)		CONSERVATIVE TREATMENT 34	
	NO.	P.C.	NO.	P.C.	NO.	P.C.
1. Dead on admission	12	75.0	33	47.1	25	73.5
2. Under 4 pounds	2	12.5	3	4.3	2	5.8
3. Stillborn	13	81.2	39	55.7	29	85.3
4. Neonatal deaths	2	12.5	4	5.7	1	2.9
5. Gross mortality (3) + (4)	15	93.7	43	61.4	30	88.1
6. Not dead on admission or under 4 pounds	2		34		7	
7. Net mortality (6)	1	50.0	7	20.6	3	42.8

At this point it may be well to consider the fetal mortality in internal hemorrhage. Seventy, or 58.3 per cent, of 120 infants were dead on admission and 7, or 5.8 per cent, were under 4 pounds. In about two-thirds of the cases, therefore, there was little or no chance of saving the baby. The net fetal mortality with pelvic operative delivery was 50.0 per cent, and the gross 93.7. With cesarean section, the net fetal mortality was 20.6 per cent, while the gross was 61.4 per cent. Under conservative treatment, the net mortality was 42.8 per cent and the gross was 88.1 per cent. (Table IV). As regards the infant, if it be alive, the advantage is with cesarean section; not so is this the case as regards the mother, as I shall demonstrate.

For at least twenty years the method of controlling the hemorrhage approved by most American obstetricians has been by cesarean section. Table V indicates that the results have been far from good. An average mortality rate of 20.5 per cent is many times that of placenta previa;

4. In 69 cases of internal hemorrhage delivered by cesarean section the death rate was 14.5 per cent.

5. In 34 cases of internal hemorrhage treated by conservative measures the mortality was 2.9 per cent.

6. Conservative measures give a better prognosis for the mother in both types of premature separation of the placenta.

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DISCUSSION

DR. WILLIAM E. STUDDIFORD, JR., NEW YORK, N. Y. (by invitation).—I fully agree that Dr. Irving's first group, which consists of those with partial placental separation, should be treated conservatively. It was a little surprising to note the large number of these cases formerly treated by cesarean section. The slight degree of placental separation present in most of these patients is evident by the fact that 19 living infants were obtained in these operations. The fetal death rate is probably increased by allowing these patients to deliver spontaneously, since the degree of placental separation may increase during the process. The maternal death rate should not be much above normal expectation. On the other hand cesarean section must inevitably lead to greater maternal risks.

The second group includes the severe type of case which is often characterized by complete placental separation and by hemorrhagic infiltration of the myometrium. While it has always seemed best to allow these patients to deliver spontaneously if possible, certain cases present such obstacles to rapid delivery that it has always seemed to me that they were best handled by cesarean section. Occasionally, due to a functionless myometrium, hysterectomy even may be indicated. It is a little startling to hear that cesarean section can be abandoned as a method of treatment in these patients.

Cesarean section with or without hysterectomy is performed, as a rule, only on the most severe cases. The mortality in this small group is of course high. It is hardly fair then to compare the cesarean section mortality based on this group with the general mortality for all degrees of placental separation.

I have had no experience with the vaginal pack and Spanish windlass. However, it might be of interest for the sake of comparison to review the results of treatment in these cases at Bellevue Hospital.

From May 1, 1934 to March 1, 1937 approximately 5,000 deliveries occurred. In this group were present 60 cases of premature separation of the placenta after the twenty-eighth week of pregnancy. Sixteen showed some evidence of toxemia. Trauma as an etiologic factor occurred once. Forty-two cases were examples of external hemorrhage, while 18 were classified as internal hemorrhage.

With only one exception all the cases of external hemorrhage were delivered pelvically. In addition 11 cases of internal hemorrhage were delivered by this route. Hemorrhage was treated by rupture of the membranes, by the occasional use of the hydrostatic bag and by transfusion. The latter procedure was utilized in 26 per cent of the patients. Out of a possible 53, 25 infants were discharged in good

the proponents of cesarean section is that it affords an opportunity to perform a hysterectomy. Table VI shows the results in 33 Porro operations appearing in the literature. The logic is not apparent which impels one to perform an operation with a 20 per cent mortality, so that he may convert it into another with twice the death rate. We have in the past performed 6 Porro operations in this type of case with 3 deaths, a mortality of 50 per cent.

TABLE VI. INTERNAL HEMORRHAGE. RESULTS WITH PORRO CESAREAN SECTION AS REPORTED BY VARIOUS AUTHORS

AUTHOR	CASES	DEATHS	PER CENT
Welz ^a	3	1	33.3
Willson	21	10	47.6
Davis and McGie	6	0	00.0
Fitzgibbon	3	2	66.7
	33	13	39.4

TABLE VII. INTERNAL HEMORRHAGE. BOSTON LYING-IN HOSPITAL. MATERNAL MORTALITY ACCORDING TO THE METHOD OF DELIVERY

	CASES	DEATHS	PER CENT MORTALITY
Pelvic operative delivery	16	3	18.7
Cesarean section	69	10	14.5
Conservative measures	34	1	2.9

Among the 69 cases of internal hemorrhage subjected to cesarean section 19, or 27.5 per cent, required transfusion, as contrasted with 4, or 11.7 per cent, of the 34 delivered by conservative measures.

Since 1931 no patient with internal hemorrhage has been delivered by cesarean section unless the infant was living and viable and the mother in good condition (Table VII). Twenty-six patients have been treated by the pack and Spanish windlass, with the one death already noted, and 8 others who entered in active labor have been left alone, with the exception of one case in which the membranes were ruptured artificially.

Our death rate for conservative treatment has been 2.9 per cent, as against 14.5 per cent for cesarean in 69 cases of the same type, or a lowering of our mortality to one-fifth of its former figure.

SUMMARY

1. Three hundred and fifty-three cases of premature separation of the placenta are reported; of these, 234 had external and 119 internal hemorrhage.
2. In 170 patients with external hemorrhage delivered through the pelvis by simple means there were no deaths.
3. In 30 cases of external hemorrhage treated by cesarean section, the death rate was 3.3 per cent.

In the first five years my treatment was active, including such procedures as podalic version, Braxton Hicks and dilatation of the cervix. For twenty-six years, however, the treatment has been wholly expectant.

RESULTS OF THE TREATMENT OF PREMATURE SEPARATION OF THE PLACENTA
IN 228 CASES

	COMPLETE SEPARATION		PARTIAL SEPARATION	
	11		3	
Rotterdam 1907-1910 (Active treatment)	Mothers dead	2	Mothers dead	0
	Children dead	11	Children dead	1
	72		53	
Rotterdam 1911-1926 (Conservative treatment)	Mothers dead	7	Mothers dead	0
	Children dead	72	Children dead	20
	44		45	
Utrecht 1927-1936 (Conservative treatment)	Mothers dead	4	Mothers dead	0
	Children dead	44	Children dead	30

This table shows the results for mother and child. The infant mortality in total separation is 100 per cent, in partial separation 50 per cent. By conservative treatment not one of the mothers with partial separation died, while of the mothers with complete separation 11 of 116 or 10 per cent died. The conservative method of treatment is morphine, and when necessary stimulants and blood transfusion.

Delivery after complete separation was accomplished one hundred times spontaneously, ten times artificially. Of the 11 women who died, 6 died before parturition, 5 from hemorrhage, 1 from uremia; and 5 after parturition, 2 from anuria, 1 after vaginal cesarean section, and 2 from hemorrhage postpartum after artificial delivery. Not a single patient bled to death after spontaneous delivery.

Regarding the causes of the premature separation: we find the frequency in normal women to be 1:22,000; in toxemia and nephritis, 1:220; in eclampsia, 1:57. There was no difference between the cases of complete and partial separation in respect to the albuminuria, the hypertension, and even the future prognosis. For out of 101 women with partial separation, 4 died more than one year after the separation from chronic nephritis or apoplexy, while out of 127 women with complete separation, 6 died. This proves that the cause of retroplacental hemorrhage lies in the vessels, and that it is accidental whether the hemorrhage is slight or considerable. On the other hand it is striking to see that all women with partial separation have recovered, while those with considerable separations have shown very severe disturbances, especially of the kidneys, and that 3 have died from anuria. Thus it is evident that the separation is not the result of the impaired kidneys but that these serious symptoms develop through the large retroplacental hemorrhages.

In my opinion the whole process develops as follows: From the products of gestation, spasms of the vessels arise with disturbed circulation. This defective circulation brings about, with the aid of the hypertension, hemorrhages in different organs and in the decidua. When arterial sinuses are opened, a severe hemorrhage may occur, accompanied by separation of the placenta and distention of the uterus. This distention may produce rents in the peritoneum and hemorrhages in the muscle. By this rapid distention furthermore, reflex spasms of the vessels occur. This reflex spasm causes the anuria, with eventual necrosis of the kidney cortex and bleeding and necrosis of the liver. In short the symptoms are the same as develop after eclamptic convulsions. These disturbances are, it is true, much more frequent in eclampsia than in the severe forms of premature separation, but this is due to the susceptibility of the tissues to disturbances in the circulation. This, in general, is less in premature separation than in eclampsia.

condition, a mortality of 55 per cent. The remainder succumbed to the causes described by Dr. Irving. There was one maternal death, a toxic patient with concealed hemorrhage and bacterial endocarditis, who succumbed four days postpartum from cardiac failure.

In only one instance did hemorrhage occur after the third stage. Again this was a patient with concealed hemorrhage and complete separation. Because bleeding could not be controlled with packing postpartum, a hysterectomy was performed, hemorrhagic infiltration of the uterus being present. One patient with external hemorrhage was delivered by cesarean section, but additional indications for the operation were present in this case.

In seven patients it was felt that the situation could best be handled by cesarean section. All of these were instances of complete separation with a dead fetus. Transfusion was used in all cases and was often repeated. In two cases the uterus did not react after the removal of the fetus and placenta and a hysterectomy was performed. There was one maternal death, which occurred fourteen days postpartum from staphylococcus sepsis in a patient treated by cesarean and hysterectomy. This patient received 3,100 c.c. of blood before and after operation.

The maternal mortality in the group treated by cesarean section amounted to 12.5 per cent; in the group delivered pelvically to 1.9 per cent; in the group as a whole to 3.3 per cent.

DR. NORRIS W. VAUX, PHILADELPHIA, PA.—My experience has led me to separate all the cases of suspected premature separation into the following groups:

1. Those cases with mild frank bleeding, whose general condition and that of the infant in utero has not yet become affected by blood loss.
2. Those cases which undoubtedly have concealed or frank hemorrhage sufficient to produce shock and collapse from blood loss. This is frequently seen in emergency cases, when the placenta has become completely detached and intrauterine fetal suffocation has occurred.

The first group should be treated conservatively, for a time at least. In the second group the immediate treatment should be directed towards combating the shock and collapse, followed by prompt radical intervention.

In the last two years at the Philadelphia Lying-In Hospital, we have felt that the proved cases of premature separation should be treated by immediate intervention by cesarean section, preferably under local anesthesia. This is directly the opposite of the methods of conservatism advocated by Dr. Irving. It has been our custom, however, to use conservatism in the cases of mild or partial separation which evidence no results of excessive blood loss, but these individuals must be kept under constant observation, and the more radical methods employed if evidence of further separation presents itself.

It is not appropriate to compare the conservative and radical policies on total groups of cases. The underlying etiologic factors, such as toxemia and associated conditions, must necessarily influence the method chosen and these affect the figures for certain methods of therapy.

As to the question of removal of the uterus after cesarean section, Dr. Irving has pointed out the added risk associated with hysterectomy, and I most heartily agree. Very rarely is this procedure justified, as the recuperative powers present in the uterine musculature are remarkable.

DR. K. DE SNOO, UTRECHT, HOLLAND.—During a period of thirty years I have observed as many as 228 cases of premature separation of the placenta. In 127 cases more than half of the placenta was separated, in 101 less than a half. Most of these latter cases were diagnosed only after birth by the finding of clots on the maternal side of the placenta. The first group, on the other hand, forms the severe cases, generally accompanied by the classic symptoms.

THE ETIOLOGY OF CONGENITAL MALFORMATIONS IN THE LIGHT OF BIOLOGIC STATISTICS*

DOUGLAS P. MURPHY, M.D., PHILADELPHIA, PA.

(From Department of Obstetrics and Gynecology and Gyneccean Hospital Institute, University of Pennsylvania)

IT IS said that development results from the interaction between inherited tendencies contained within the egg substance itself, and the external conditions which surround and act upon this substance (Stockard).¹

It is common knowledge that many congenital abnormalities are inherited. The question arises, however, as to whether all defects have their origin in this manner, or whether some of them may be due to disturbances within the environment of the otherwise normal ovum.

A number of observations support the idea that man can influence the environment of the ovum sufficiently to modify its growth. Stockard¹ subjected the eggs of fish, during early stages of development, to the action of weak solutions of alcohol. The resulting embryos exhibited marked abnormalities in the structure of the central nervous system and organs of special sense. Bagg² likewise modified the growth of the eye and brain of rat embryos by exposing them to radium irradiation. Murphy³ assembled evidence that radium and roentgen exposure will arrest the growth of the human embryo, microcephaly being the most common sequel.

With respect to spontaneously occurring malformations, Mall⁴ found a high incidence of abnormalities among aborted, human embryos, and ones from tubal gestations. The very large number of pathologic embryos found in the tubal pregnancies was one of the strongest arguments to him that they were not the result of germinal influences, but due to unsuitable external conditions.

It is conceivable, however, that the pathologic embryos examined by Mall, may have acquired their unusual maternal relationships as a result of abnormal germinal characteristics. In such an event, the ensuing maldevelopment would have been due primarily to hereditary causes.

It is generally agreed, therefore, that many congenital malformations are inherited, also that the development of the ovum can be modified under experimental conditions. The evidence does not appear to be entirely convincing, however, that spontaneously occurring abnormalities can be due to environmental factors. The present report deals with certain characteristics of a series of families possessing congenitally

*Read, by invitation at the Sixty-Second Annual Meeting of the American Gynecological Society held at Swampscott, Mass., May 31 to June 2, 1937.

DR. RUDOLPH W. HOLMES, CHICAGO, ILL.—Spiegelberg over seventy-five years ago clearly demonstrated that not rarely (about 1 in 200 deliveries) inspection of the placenta postpartum reveals flecks of blood, up to the size of a goose's egg, of a dirty putty-like appearance, which are clots in which the hemoglobin has been destroyed. These produce no clinical signs, or at most trivial symptoms which are not recognized. From such insignificant entities we run the gamut of every degree of placental separation up to complete ablation, and every degree of hemorrhage up to those obstetric cataclysms, ushered in by profound hemorrhage or those severe cases of *Couvellaire apoplexy*. In both these types there may be not one drop of blood escaping from the vagina.

I have never conceded that those cases of ablation without external bleeding carry a higher mortality rate for mother and baby than the open type. The only difference lies in the fact that the diagnosis is delayed in instances of *absolute concealment*. On the other hand, in the open hemorrhages, the amount of blood which escapes is never the criterion of the amount which has left the circulation. I firmly believe that we should divide all instances of ablation into *absolute concealment* and *relative concealment*. I have tabulated all the symptoms which are reputed to occur with ablation placentae. Each and every sign and symptom so recognized prevails with equal frequency in the occult and overt types, except that external bleeding is constant in the latter.

If we concede for the moment that absolute concealment does carry an inherent jeopardy wanting in the relative types, then we should concede that the tampon is entirely contraindicated for it immediately converts the open into a concealed type. But, we know that for over 150 years the Dublin School has employed the tampon for "accidental hemorrhage" with signal success. I heartily substantiate Dr. Irving's stand in the use of the tampon in selected cases. I would also raise my protest with that of Dr. Irving that a routine cesarean section for all instances of ablation is inexcusable.

In my personal experience of 26 instances of severe clinical ablation placentae, I have found that the hemorrhage and uterine changes produce with rare exceptions a marked cervical relaxation, a dilatable os. I voice this view with great timidity in view of the present reaction to manual dilatation, but I feel that most ablations may be delivered by manual dilatation and version (vel forceps or craniotomy) far more quickly than is possible in waiting for the "set up" and then performing a cesarean section.

DR. IRVING (closing).—Of the 119 cases I reported that fall into the internal hemorrhage group, some had complete separation and some did not. It is not always possible to tell whether the separation is complete or whether it is partial.

The 119 cases fell, however, into the same group as those discussed by Dr. Studdiford and Dr. Vaux. We felt just as they did until we abandoned cesarean section in 1931. Our conversion to conservative measures was due to the 16 cases of Dr. Polak. This method lacks rapidity but I am not willing to admit that it is less safe than cesarean section. In our own hands it has been much safer.

I would like, to take exception to Dr. Holmes' statements regarding manual dilatation. That method has been anathema to me ever since I was an interne and I have taught that it is one of the most fatal maneuvers in obstetrics.

Pelvic disease relates to any pelvic condition for which the mother received treatment prior to the conception of her defective child. Pre-conceptional douching deals with the use of contraceptive chemical douches employed at the time that the malformed child was conceived. Although no control data were available, the attributes in Table III did not appear to occur unusually often.

TABLE I. CLASSIFICATION OF CHIEF DIAGNOSES BY BODY SYSTEM

Showing the location of one malformation for each defective individual, arranged according to body system. In case two or more defects were present, the most serious one was selected. Note the great frequency of malformations involving the nervous system.

BODY SYSTEM	INDIVIDUALS	
	NUMBER	PER CENT
Reported	935	100.0
Nervous	566	60.5
Gastrointestinal	140	15.0
Bones, muscles, skin	103	11.0
Cardiovascular	80	8.6
Monsters not described	28	3.0
Genitourinary	10	1.1
Ill-defined	4	0.4
Respiratory	3	0.3
Unstated	1	0.1

TABLE II. NERVOUS SYSTEM DIAGNOSES

Showing the nervous system defects according to diagnosis. Note the seriousness of the malformations, and the great frequency of hydrocephalus and spina bifida.

DIAGNOSIS	INDIVIDUALS	
	NUMBER	PER CENT
Reported	566	100.0
Hydrocephalus alone	180	31.8
Spina bifida alone	112	19.8
Anencephalus	98	17.3
Hydrocephalus with spina bifida	93	16.5
Meningocele	26	4.6
Craniorachischisis	25	4.4
Microcephalus	13	2.3
Encephalocele	8	1.4
Mongolism	8	1.4
Others	3	0.5

TABLE III. FAMILIAL CHARACTERISTICS RELATING TO ENVIRONMENT

Showing the frequency with which some of the familial characteristics relating to environment as a possible etiologic factor, were observed. Note the relative infrequency of these attributes.

CHARACTERISTIC	FAMILIES STUDIED NUMBER	CHARACTERISTIC PRESENT PER CENT
Chronic illness of Father	569	9.3
Chronic illness of Mother	640	8.8
Positive maternal Wassermann	324	12.4
Previous maternal pelvic disease	628	10.8
Previous atypical menstruation	654	12.5
Preconceptional douching	345	25.5

malformed children. These are presented in order to show the apparent influence, and relative importance, of heredity and environment as factors in the production of congenital defects in man.

MATERIALS AND METHODS

The material forming the basis for the study was secured in the following manner:

There were found in the files of the Bureau of Vital Statistics, Department of Health of the State of Pennsylvania, 130,132 death certificates for stillborn and liveborn individuals who died in Philadelphia during the five years between Jan. 1, 1929, and Dec. 31, 1933. Each of these certificates was examined and among them were found 1,476 cases of congenital defect.

The deceased individual was considered to have possessed an abnormality under either of two conditions: (1) if the malformation involved the surface of the body, or, (2) if internal, its presence had been disclosed by operation or necropsy. Diagnoses not conforming to these requirements were considered as not verified and were excluded from further consideration. This procedure gave 890 cases for study. An attempt was made to interview the mother of each individual, the visits being carried out in the summer of 1934, by three fourth-year medical students. By this means, forty-five additional malformed brothers and sisters of the defective offspring were located, giving information upon a total of 935 defective individuals. Since approximately 80 per cent of the deformed persons were born in hospitals, these institutions were visited, and pertinent facts were extracted from their records.

THE DATA

The location of the *chief* malformation of each individual by body system is recorded in Table I. The diagnoses of the largest single group appearing in Table I, are given in Table II. The seriousness of the defects is indicated by the fact that 90 per cent of the individuals died within a year of birth.

The familial characteristics having a possible bearing upon the etiology of the physical abnormalities are considered under two headings: (A) environment and (B) heredity.

(A) ENVIRONMENT

The frequency with which certain of the environmental characteristics occurred is given in Table III. In this table, the term "chronic illness" refers to sickness which existed at the time that the malformed child was conceived. The Wassermann reactions are those which were taken when the mothers were pregnant with their malformed offspring.

Relative Sterility Before Birth of Malformed Child.—The lengths of the intervals occurring between 2,146 pregnancies of the mothers of malformed children were determined.¹² A long period of relative sterility occurred *four times more often*, immediately preceding the conception of malformed offspring, than it did preceding the births of the normally developed brothers and sisters. This is interpreted as indicating that at this time the germ cells were too abnormal for fertilization to occur.

Frequency of Malformations Among Brothers and Sisters.—Two hundred and seventy-five mothers became pregnant *after* the births of their defective children.¹³ The incidence of malformation among these subsequent offspring was approximately 18 to 25 times greater than in the population-at-large.

Duplication of Malformations Among Brothers and Sisters.—Forty families each possessed two or more congenitally malformed children.¹⁴ The defect observed in the first malformed child reappeared in a subsequent, malformed brother or sister in 46 per cent of instances.

Duplication of Malformations Among Distant Relatives.—In 39 cases, a distant relative of the malformed child exhibited a congenital malformation.¹⁴ The latter defect was identical with that observed in the malformed child in 41 per cent of instances.

Duplication of Rare Defects.—Maldevelopment occurs more frequently in the left dome of the diaphragm than in the right dome. One mother gave birth in successive pregnancies to two children both exhibiting an absence of the *right* dome.¹⁴

Duplication of Defects Through Two Wives.—One father had a child with a right-sided harelip and cleft palate by each of two wives.¹⁴

Malformations According to Sex.—The ratio of males to 100 females, among the malformed children, and their normally developed brothers and sisters, is given in Table IV. Hydrocephalus, pyloric stenosis and harelip seemed to favor the males, while anencephalus was found more frequently among females.

TABLE IV. SEX RATIO

Showing the proportion of males to females among offspring in families having malformed children. Note preponderance of defective *males* in individuals with *hydrocephalus*, *pyloric stenosis*, *hare lip* and *cleft palate*; and the large number of *females* exhibiting *anencephalus*.

DESCRIPTION	MALES	FEMALES	MALES TO 100 FEMALES
Normal siblings	851	694	122.6
Malformed offspring	501	434	115.4
Hydrocephalus without spina bifida	114	67	170.0
Pyloric stenosis	49	16	306.0
Hare lip, cleft palate	30	16	187.5
Anencephalus	27	74	36.5

DISCUSSION

The above observations offer no evidence that environment plays a rôle in etiology. This may be due to limitations of the study. For example, such defects as amputations, which are believed to be due to amniotic bands, did not appear in the series of abnormalities which formed the basis for this report.

Frequency of Reproduction.—Two hundred and eight families each had two or more children born before the birth of the congenitally malformed child.⁵ Reproduction occurred in this group no more frequently than in a series of control families having normally developed offspring.

Month of Conception.—The month of conception of 935 malformed individuals was studied.⁶ The greatest frequency of these conceptions occurred in the summer months. This was contrary to the findings of Petersen,⁷ who observed the greatest incidence in the winter and spring months. These findings indicate that there is no unusual seasonal occurrence in the time of conception of congenitally malformed individuals.

Diet.—The diet of 545 mothers was investigated. The important foods, such as milk, leafy vegetables, fruits, and whole grain breads were not used by these mothers in amounts sufficient to meet the mineral and vitamin standards, as generally recommended for pregnant women. The most obvious dietary deficiencies were in calcium, phosphorus, iron and vitamins B and C. Accurate control figures for these observations, however, were not available.

Coincidence of Malformation with Placenta Previa.—Placenta previa occurred only once in 741 malformation pregnancies. Its frequency in the general population, according to Williams,⁸ is about one in 1,000 cases in private practice. It is possible that no additional instances of placenta previa would have been met had 1,000 malformation pregnancies been studied.

(B) HEREDITY

Color.—There were 814 white and 76 negro, malformed individuals. These figures gave a ratio of 5.72 malformed whites per 1,000 white livebirths, and 3.17 malformed negroes per 1,000 negro livebirths occurring in Philadelphia during the five-year period in question. The rate for the whites, therefore, was nearly twice that for the colored. This racial selectivity of malformations is borne out by governmental statistics.⁹

Maternal Age.—Data dealing with the ages of 570 mothers at the births of 607 malformed children, and 1,583 normally developed siblings were available for analysis.¹⁰ The proportion of defective to normal offspring at different maternal ages was found to be as follows: (a) lowest when the mothers were between twenty and twenty-five years of age; (b) more or less constant when the mothers were between fifteen and thirty years of age; (c) increasing from year to year when the mother had passed thirty; (d) greatest after the mothers had passed forty years of age, at which time the ratio of defective to normally developed children was approximately three or more times that noted before the mothers were thirty years old.

Birth Order of Miscarriages, Premature Births, and Stillbirths.—One hundred and fifty-one families experienced one or more miscarriages, premature births, or stillbirths.¹¹ These unsuccessful pregnancies occurred before and after the birth of the malformed offspring, more often than they did preceding and following the births of the normally developed brothers and sisters. The development of the resulting offspring is unknown, nor is it understood to what extent malformations are associated with miscarriages, premature births, and stillbirths. Mall⁴ has shown that many aborted embryos are malformed, and the present study indicates that at least 25 per cent of malformed individuals are stillborn. There is reason, therefore, to believe that at least some of the unsuccessful pregnancies may have given rise to malformed individuals. Regardless of the development of the offspring, miscarriages, premature births, and stillbirths would seem to represent expressions of reproductive inefficiency.

DISCUSSION

DR. WILLIAM A. SCOTT, TORONTO, ONT.—In attempting to evaluate “environmental” and “hereditary” factors, it is necessary to define rather precisely just what is meant by the terms. For instance, Muller subjected the fruit fly to the action of x-rays and produced gene mutations that had previously arisen spontaneously in fly colonies. The treated flies, however, showed 150 times more mutations than the untreated controls. These mutations, of course, were due to “environment,” but, as they bred true to type, the changes in their offspring were the result of “hereditary” causes. What began from environment became hereditary. If we wish to try and separate such factors should we not think of them as falling into three possible groups? 1. Hereditary factors, affecting the chromosomes and being transmitted as either dominant or recessive characteristics. 2. Constitutional factors, affecting the germ plasm before fertilization. 3. Environmental factors, affecting the development of the ovum after fertilization. It would be understood, of course, that experimental work has shown that external influences may affect any one of these classes.

Dr. Murphy has shown that “disturbed pregnancies” occur more frequently than would be expected by chance in the pregnancies immediately preceding and immediately following the pregnancy which ended in the birth of the defective child, and Mall has pointed out that many aborted embryos are pathologic. Two explanations of this are possible. Faulty implantation of the ovum may result in deficient nourishment and injury to some of the cells of the early ovum, or an abnormal ovum may tend to have poor implantation and be liable to abort.

During the last two years we have had 16 cases of fetal deformities and one of hemorrhage of the newborn, the latter following elective cesarean section. Two of these were complicated by placenta previa (12.5 per cent) and one by threatened abortion. In these cases, therefore, there were over 18 per cent with complicated pregnancies. Yet, during the same period, the incidence of fetal deformities was only 0.9 per cent of the total births. Our incidence of placenta previa was about the same as Dr. Murphy's, namely 24 cases or 0.8 per cent of total deliveries. In the same series, there were 18 cases of macerated fetuses, 14 of whom had complicated pregnancies, in 9 the complication being toxemia of pregnancy.

Some hereditary deformities are manifested only when marriage occurs between suitable persons. I have a patient with two normal babies. She was one of a family of six, all of whom had either unilateral or bilateral congenital hip disease, yet in a careful inquiry no evidence of the disease could be discovered in the families of either her father or mother. It would appear that this tendency is a recessive characteristic of both her father and mother.

Without figures to substantiate my opinion, I have had the impression that certain types of fetal abnormalities, particularly mongolian idiocy, tend to arise in pregnancies occurring in the latter part of the childbearing period.

One occasionally sees cases where there appears to be a combination of hereditary and environmental factors. One of my patients gave birth to a baby with an amputation of the right leg just above the knee. This is usually accepted as an environmental occurrence, but the same child had an absence of the anterior chest and abdominal walls and an imperforate anus. She has since had a normal child.

It was very surprising to learn that the percentage of deformities in white people was double that of the colored race. With the close intermarriage of the latter, one would have thought the tendency to malformations would have been accentuated.

DR. WILLIAM R. NICHOLSON, PHILADELPHIA, PA.—I am interested in the type of malformation in which you cannot find any inheritance factor. Many years ago I delivered a patient whose family had a perfectly normal history so far as malformations were concerned. The mother had had one child by a former husband, who

On the other hand, the remaining characteristics bearing upon etiology, all point to heredity as the most likely cause of malformation. These fall into four groups: (a) color, (b) sex ratio, (c) reproductive inefficiency and (d) the character of the defects which were seen in brothers and sisters.

Abnormalities were observed in white persons twice as often as in negroes, which fact would support the theory of a germinal origin for congenital defects. This high frequency of malformations in whites is of interest in view of the fact that syphilis is much more common in negroes. It might be concluded, from these observations, that syphilis is not an etiologic factor.

Certain defects afflicted one sex more often than the other. If spontaneously occurring malformations arise, primarily, from environmental influences, it would seem that the sexes should be affected with equal frequency.

Reproductive inefficiency was indicated by: (a) the long period of relative sterility frequently observed immediately preceding the birth of the malformed child, (b) the nearness of miscarriages, premature births and stillbirths to the malformation pregnancy, (c) the high incidence of malformed offspring born to older mothers, and (d) the increased frequency of congenital defects among brothers and sisters. Since these evidences of reproductive weakness, in very many cases, operated over a period of years, it seems likely that their origins rested upon defects within the germ cells, rather than upon abnormality in the environment.

Perhaps the single most convincing piece of evidence in favor of heredity is the frequent duplication of defects in brothers and sisters. This was observed in the case of the more unusual, and more serious malformations, as well as in the more common types of less serious ones.

From this investigation it is *not* possible to conclude that *spontaneously occurring*, human, congenital malformations *do not* arise from factors inherent in the environment of the ovum. On the other hand, no evidence was found to confirm this theory. All of the available data point to heredity as the cause of maldevelopment.

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THE CONTINUOUS AUSCULTATION OF THE FETAL HEART BY MEANS OF AN AMPLIFYING STETHOSCOPE*

PRELIMINARY REPORT

HARVEY B. MATTHEWS, M.D., F.A.C.S., BROOKLYN, N. Y.

(From the Department of Obstetrics and Gynecology, Methodist Episcopal Hospital)

THE importance of the continuous auscultation of the fetal heart during labor, and particularly during delivery, is unquestionable. Early manifestations of fetal distress could be more often recognized if it were possible to auscultate the fetal heart continuously. The uncertainty and shortcomings of present-day methods are well known and keenly appreciated.

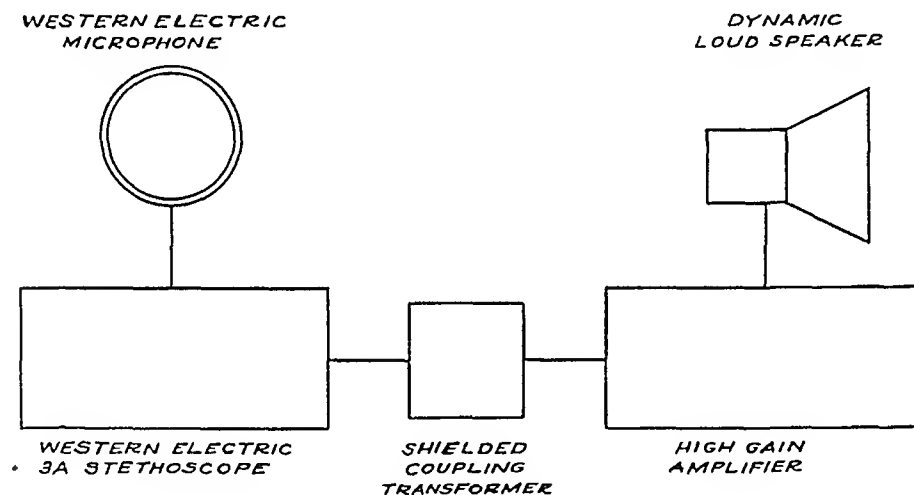


Fig. 1.

There have been many methods and systems devised for recording the fetal heart tones but up to the present none of these have proved satisfactory. They are, for the most part, too complicated and expensive for general use.

Because of the vast improvement in sound reproduction, all experiments prior to 1927 can be disregarded, although the experimental results with the various types of fetal cardiographs are pretty well borne out by modern methods of sound reproduction.

The first investigator to use modern methods of sound reproduction for recording the fetal heart tones was Dr. T. Cioslowski, of Warsaw (1932). His apparatus consisted essentially of: (1) microphone, (2) amplifier, (3) a more powerful amplifier, and (4) ear phones or megaphone. This apparatus was demonstrated

*Read at the Sixty-Second Annual Meeting of the American Gynecological Society, held at Swampscott, Mass., May 31 to June 2, 1937.

was perfectly healthy. In this labor she delivered a child with agglutination of the toes and fingers, a microcephalic head with some hydrocephalus. Subsequently this patient had two perfectly normal children by the same husband. The interesting point in the history was that at the time this woman began her pregnancy she had a very queer undiagnosed condition of fever.

I contend therefore that developmental irregularities in these children may be due to acute disease of the mother.

I would include in the eight classes as given by Dr. Murphy, not only chronic disease but certain types of acute disease as well.

Looking over my statistics, upon the work of the midwives of Philadelphia since 1914, I found among the 96,000 cases which we have delivered 184 deformities among the children. Strangely enough, while Dr. Murphy states that he has had no amputations, in our list we had 7 amputations, none of which we thought were due to amniotic bands.

DR. JOSEPH B. DE LEE, CHICAGO, ILL.—During the 1918 influenza epidemic quite a number of monstrosities occurred in my own practice and in that of others. It was noticed that these women had had the "flu" in the early part of their pregnancies.

Dr. Williams, a veterinarian of Cornell University, reports that cattle on the range produce fewer monstrosities than cattle that are held under so-called civilized and wholly modernized conditions.

DR. EMIL NOVAK, BALTIMORE, MD.—Among the hereditary factors which Dr. Murphy enumerated is one which he spoke of as reproductive deficiency. In cases of endocrinopathic sterility I have been impressed with the relative frequency of congenital fetal deformities in those patients in whom pregnancy has occurred, perhaps after long-continued treatment. For example, a woman of about forty finally conceived after a primary endocrinopathic sterility of seventeen years, and at full term was delivered by cesarean section of a child which died shortly after birth of congenital cardiac abnormality. In another recent endocrinopathic case, pregnancy occurred after several years' treatment for sterility, but the baby was an anencephalic monster. And I might enumerate still other cases of this type. Such experiences are inclined to temper, at least slightly, one's enthusiasm in the treatment of endocrinopathic sterility.

complicated affair and utterly unsuited for general use. It should, however, be stated in fairness to Professor Nota, that his method is very accurate and valuable in detecting pathologic defects in the fetal, as well as maternal, heart tones.

We have strived to devise a system for the continuous auscultation of the fetal heart by means of an amplifying stethoscope.* To carry out this idea we have employed a Western Electric No. 3A stethoscope with a dynamic microphone of contact type. The microphone is encased in sponge rubber with convenient attachments for fastening it to the patient's abdomen. The output of the Western Electric stethoscope is fed into a specially shielded coupling transformer and the output of this transformer is in turn fed into a high gain amplifier which drives a 10-inch dynamic loud speaker. The loud speaker is insulated from acoustic feed-back into the microphone which otherwise would cause a "howl" and destroy the desired fetal heart beats. With such a "hook-up" the fetal heart tones can be heard continuously for any length of time (Fig. 1). After placing the microphone over the fetal heart, i.e., over the area of the mother's abdomen where the fetal heart sound is loudest, the operation is simple; plug in; tune in; and listen (Figs. 2 and 3).

This system is far from perfect. It is expensive and somewhat cumbersome and therefore not generally practical, even for hospital use. However, we believe that the idea is right and already have plans for a much more compact and therefore easily portable system which will be far less expensive and much more efficient.

I wish to express my sincere appreciation to Dr. Albert Hersheimer, Resident Obstetrician, who has given many excellent suggestions and rendered very valuable assistance throughout this work.

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643 ST. MARKS AVENUE

(The Transactions of the American Gynecological Society are included in the November issue, excepting the papers by Drs. J. R. Goodall, K. M. Wilson, and Prof. K. de Snoo.)

*This work was made possible through a grant from the Lindridge Fund of the Department of Obstetrics and Gynecology.

before the Gynecological Society of Warsaw in 1932. The instrument did not meet with favor and has not, to my knowledge, been put on the market for general use.

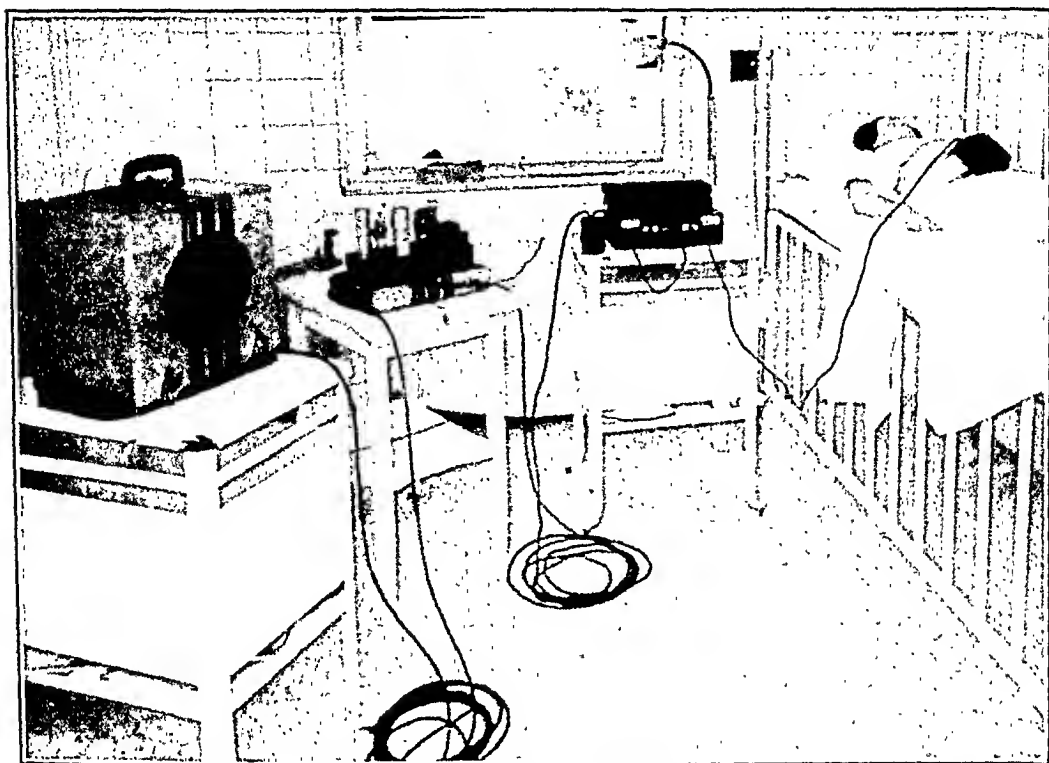


Fig. 2.

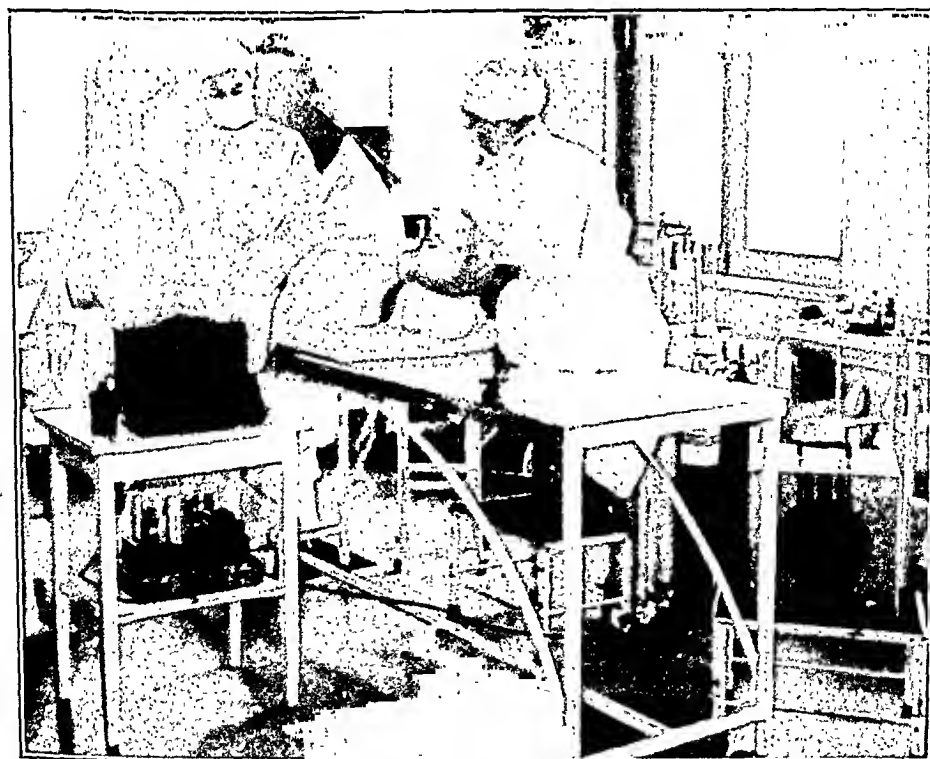


Fig. 3.

Another system, devised by Fillippo Nota, called "the electro-acoustic registration of the fetal heart tones by means of a constant density system" (1934), is a very

remains at about 16 per thousand because of the extension of the indications for cesarean section. The mortality of primary section for uncomplicated disproportion or cervical dystocia is now about 1 per cent. The mortality of repeat operations is now about 3 per cent. That the mortality in general is now about 4.5 per cent is due mainly to the high death rate in primary section on patients with impaired cardiac or renal function. The infant mortality varies according to the group considered. For disproportion it has been about 2 per cent for the past 16 years, about half the deaths being due to congenital anomalies. In the group of repeat sections during the same period fetal mortality has been nearly 4 per cent, the increase being due mainly to the larger number of premature infants delivered by repeat operations. In the groups of toxemic, nephritic, and cardiac patients there is a high neonatal death rate due to prematurity, which raises some doubt as to whether cesarean is any better than pelvic delivery for these premature infants.

WM. C. HENSKE.

Hudnall Ware, H., Jr.: Cesarean Section in Richmond, Virginia, Virginia M. Month. 63: 82, 1936.

This is a statistical survey of the 127 cesarean sections done in Richmond during a five-year period. The figures show that the number of sections increased from 4.2 to 9.4 per thousand births between the first and last years of the study, the average incidence being 2 per cent of all hospital deliveries. The mortality was 8.8 per cent. The author draws the following conclusions from his figures: The duration of labor and rupture of membranes are important factors in increasing the maternal mortality following section. The maternal mortality rate was materially reduced by the use of the two-flap low cervical operation, particularly in potentially infected cases. The mortality rate was 8.60 per cent for primiparas and 1.81 per cent for multiparas.

EUGENE S. AUER.

Bue, Palliez, and Gernez: The Low Cesarean Section at the Charité Obstetrical Clinic During the Last Five Years, Bull. Soc. d'obst. et de gynéc. 26: 202, 1937.

The authors report a consecutive five-year series of 131 low cervical cesarean sections which were performed without any maternal death. These cases represented an incidence of 2.47 per cent in a series of 5294 labors. The fetal death rate among these 131 sections was 6.87 per cent. In 101 cases spinal anesthesia was used and it yielded excellent results in three-fourths of the instances. The authors believe their favorable results are attributable at least in part to the use of spinal anesthesia.

J. P. GREENHILL.

Voron, Brochier, and Boulez: Fourteen Cases of Hysterotomy for Placenta Previa in the Obstetrical Clinic of Lyon, Bull. Soc. d'obst. et de gynéc. 25: 475, 1936.

The authors report 14 cesarean sections performed for placenta previa since September, 1932. All were done under spinal anesthesia except two in patients who had a severe anemia with hypotension; the anemia was so severe that transfusions had to be given during operation. All of these cesarean sections were of the low, cervical type in spite of the fact that the placenta was in the lower uterine segment. There was not a single maternal death. Hence, the authors believe that this operation is the procedure of choice in serious cases of placenta previa.

J. P. GREENHILL.

Department of Reviews and Abstracts

CONDUCTED BY HUGO EHRENFEST, M.D.

Selected Abstracts

Cesarean Section

Hoffström, K. A.: A Series of 100 Cesarean Sections, *Acta obst. et gynec. Scandinav.* 14: 1, 1934.

From 1906 to 1933, 100 cesarean sections were performed among 20,892 women at the Lying-In Hospital in Tammelfors, giving a frequency of 0.5 per cent. This figure has, however, increased during the last three years, amounts now to 1.8 per cent. Classic operations were performed 36 times, cervicocorporeal 56 times and the purely cervical operation 8 times. No complications ensued in 73 per cent of the cases. The puerperal morbidity amounted to 27 per cent and comprised 24 cases with mild and 2 with grave puerperal disturbances. Five cases terminated fatally but none of them had any connection whatsoever with the operation. Hence the operation mortality is zero. The corrected mortality for the child was 1 per cent. The following three indications were the chief causes for the operation: (1) Disproportion between the infant's head and the pelvis, (2) profuse hemorrhage from placenta previa while the cervical canal was still undilated, and (3) eclampsismus and eclampsia in which a purely expectant treatment or a conservatively active treatment was unsuccessful or in which the eclampsia was of very grave character.

Seventeen patients became pregnant again after a comparatively short time. Six of these cases terminated spontaneously.

J. P. GREENHILL.

Smith, Judson A.: Cesarean Section at the Boston Lying-In Hospital, *Surg. Gynec. Obst.* 57: 621, 1933.

From 1894 to 1931, inclusive, 1,556 cesarean sections were done at the Boston Lying-In Hospital, with a mortality of 4.9 per cent. Of these, 913 were primary sections. Of the primary sections 527 (58 per cent) were done for disproportion or cervical dystocia without other indications or complications. At the present time only about one-third of the primary sections are for this indication. Of the other primary sections 95 were performed chiefly for heart disease, 73 for toxemia or nephritis, 76 for premature separation of the placenta (including some toxic cases), 44 for placenta previa, and 98 for a variety of miscellaneous indications. The use of cesarean section for cardiac patients who have not had heart failure and have no other indication has diminished. The use of section delivery for placenta previa has increased. The incidence of primary sections for disproportion or cervical dystocia has decreased from a peak of 12 per thousand deliveries 15 years ago to a level of 5 per thousand deliveries during the past 4 years, indicating a much more conservative attitude. The total incidence of sections has been close to 30 per thousand deliveries for the last 16 years.

About one-half of the cesarean sections now are repeat sections. Although fewer cesareans are done now for suspected disproportion the incidence of primary section

In a series reviewed here the mortality rate was 6.6 per cent. The gross mortality rate following childbirth in England and Wales is 0.45 per cent. The mortality rate in 1,763 cases of cesarean section performed in England in famous maternities by experienced and distinguished operators was 5.8 per cent. The author states that the foremost reason for the widespread use of the operation is the purely surgical outlook upon obstetric problems. The baby is aimed at to be "let out" like pent-up pus by the surgically wise but obstetrically foolish.

The author believes that nature's powers and technique are safer and nature's way of overcoming moderate degrees of disproportion infinitely greater than we imagine to be the case and that a trial labor cannot truly be called such, until true second-stage pains have been present for some time.

F. L. ADAIR AND S. A. PEARL.

Crichton, E. C.: Indications for Cesarean Section, South African M. J. 8: 595, 1934.

The author devotes the bulk of the article to the relative indications.

Because of the relatively high maternal mortality in the series of sections investigated by the author (11.5 per cent) he feels that cesarean section has a minor place in the treatment of placenta previa which gives only a 4.75 per cent maternal mortality when treated by the Braxton Hicks method.

In eclampsia sections should only be employed in cases of disproportion and in rare cases which have improved under conservative treatment but appear to be in imminent danger of recurrence of severe symptoms.

In heart disease the author prefers delivery by the natural route supporting the patient with morphia in the first stage and expediting the second stage with forceps under chloroform anesthesia.

The author believes that patients who previously had a section for any reason other than disproportion may be subjected to a test of labor.

Where disproportion exists the author believes in a test of labor. If the head is descending and the cervix is dilating, the author waits until the cervix has been dilated for an hour before deciding upon the method of delivery.

If the head remains high he resorts to a lower segment cesarean section.

F. L. ADAIR AND I. C. UDESKY.

Jensen, Julius: The Management of Heart Disease in Pregnancy, South. M. J. 29: 572, 1936.

The management of heart disease in pregnancy is guided by the state of compensation. Most women with heart disease bear children without added discomfort. With close prenatal supervision patients with early decompensation will be detected. This is important because congestive failure advances rapidly in pregnant women.

When cardiac failure develops, it should be treated first by bed rest, and digitalis and morphine used as indicated. With too prolonged bed rest cardiovascular tone is impaired. The patient who does not improve upon this regime to the extent where she can withstand moderate physical effort should not go to spontaneous labor.

Early interruptions of pregnancy for cardiac reasons are rarely indicated. Premature induction of labor insures a favorable proportion between the maternal pelvis and the child and is, therefore, often advisable. Where sterilization is indicated, delivery may be effected by cesarean section.

ARNOLD GOLDBERGER.

Trillat, P.: The Treatment of Placenta Previa by Low Cesarean Section, *Bull. Soc. d'obst. et Gynéc.* 25: 715, 1936.

Among 16,500 deliveries the author encountered 104 cases of placenta previa. The maternal death rate in this series was 10.5 per cent. Ten cesarean sections were performed without any deaths. The entire fetal mortality was 67.7 per cent but among the 10 cesarean sections there was only one fetal death, hence the fetal mortality for the cesarean section group was only 10 per cent. Because of these good results, the author has performed more cesarean sections for placenta previa during the last few years.

J. P. GREENHILL.

Brindeau, A.: The Different Types of Anesthesia for Cesarean Sections, *Paris méd.* 25: 499, 1935.

The author reports a series of 100 cesarean sections performed under spinal anesthesia. This anesthesia proved entirely satisfactory in 84 cases but in 12 others general anesthesia was necessary. There were no deaths nor serious complications in this series. However, in the years preceding this group of sections, the author encountered three deaths during operation following spinal anesthesia. In spite of these sudden deaths, Brindeau believes that spinal anesthesia is the ideal one for cesarean section. He recommends local infiltration anesthesia for very sick women, for abdominal hysterotomies before full term and for the ligation of the fallopian tubes to produce sterility. He reserves general anesthesia for women who refuse spinal anesthesia, in whom lumbar puncture cannot be carried out and for those in whom spinal anesthesia does not produce satisfactory anesthesia.

J. P. GREENHILL.

Ginglinger, A.: The Type of Anesthesia Employed for Cesarean Section, *Bull. Soc. d'obst. et de gynéc.* 26: 367, 1937.

Among 237 cesarean sections performed under ether anesthesia, there were 4 deaths which Ginglinger believes could be attributed to the anesthesia. Two of these deaths were due to bronchopneumonia and two to hemorrhage produced by atony. The latter two patients died on the operating table. Among 248 cesarean sections done under spinal anesthesia there were three deaths due to immediate syncope after the introduction of the anesthetic. The author urges that local anesthesia should be used for cesarean sections. Ether should be reserved for urgent cases such as placenta previa and prolapse of the cord. Spinal anesthesia should be used only in obese women where difficulties may be encountered during operations.

J. P. GREENHILL.

Banister, J. Bright: Present Position of Cesarean Section in Obstetric Practice, *Brit. M. J.* 2: 1143, 1935.

The author believes that cesarean section occupies an unjustifiable position in obstetric practice today, that the incidence of the operation is far too high, that the indications for its use are at present too wide, and that it is attended by too high a maternal mortality rate. Such belief is supported by figures from several clinics, and by the widespread indications for the operation as cited by Amand Routh—in all, twenty-four indications under the main headings of (1) obstruction to labor, (2) uterine hemorrhage, and (3) constitutional crises.

therefore, there is less danger of shock and sepsis. Convalescence is smoother. The suture line is low down and less likely to cause adhesions between omentum, bowel or uterus and abdominal wall. The operative technique is outlined, and the recommendation for preoperative x-ray study is made.

F. L. ADAIR AND S. A. PEARL.

Basden, Margaret M.: Caesarean Section in Infected Cases, *Brit. M. J.* 1: 358, 1936.

A series of 45 cases over 11 years is reported. Some were frankly infected, others potentially so. No mortality occurred in this series.

The author believes the pendulum has swung too much in the direction of conservatism, and that though there are definite risks present, there is still a possibility of saving a certain number of infants and mothers by performing the operation in potentially infected cases. The possible dangers of a difficult instrumental delivery are not always realized. Case records are given. The low cervical operation was done in 16 cases only. The author performs this operation more commonly at the present time. Two cases had cesarean hysterectomies. This is advocated when the risk of infection appears very great.

F. L. ADAIR AND S. A. PEARL.

Gustafson, Gerald W.: An Eight-Year Survey of Cesarean Sections at the William H. Coleman Hospital, *Surg. Gynec. Obst.* 64: 1035, 1937.

The greatest single factor in the reduction of cesarean section mortality at the Coleman Hospital has been the wider adoption of low cervical cesarean section.

The low cervical operation is safer than the classic, not only in cases of patients having had tests of labor but also in elective cases. In the latter type of patients and in other patients having short lower uterine segments, the transverse incision with the Phaneuf technique is a very satisfactory procedure.

It is reasonable to assume that if low cervical operations could be substituted for the classic operations in this country, the mortality from abdominal deliveries would be cut in half.

WM. C. HENSKE.

Pemberton, John: Six Cesarean Sections on the Same Patient, *Lancet* 2: 1039, 1936.

The report of six cesarean sections on a single patient is unusual. In the last sixteen years one physician has done all six sections on this patient for a generally contracted pelvis. Each operation was elected about ten days before the estimated term date. There was only one abdominal sear and no omental or bowel adhesions, although the uterus was adherent to the abdominal wall. All puerperal periods were afebrile. The uterine wall was not unusually thin at the site of the sear.

References are made to one case having seven cesarean sections, another six.

H. CLOSE HESSELTINE.

Thiessen, P.: The Avoidance of Complications in Cesarean Sections Performed Under Spinal Anesthesia, *Med. Klin.* 32: 416, 1936.

The author describes his technique for spinal anesthesia in performing cesarean sections. He believes that this form of anesthesia is excellent for cesarean sections and is without any danger. However, one must be careful to observe all precautions.

J. P. GREENHILL.

Andrews, C. J., and Nicholls, Richard B.: Unusual Indications for Cesarean Section, Virginia M. Month. 63: 33, 1936.

The authors present a series of 1,200 consecutive deliveries with a cesarean section incidence of 2.7 per cent, or 34 cases, with no maternal mortality. They have listed as unusual indications for section all cases outside of those with a contracted pelvis. The unusual indications were: Distocia following intrauterine radium applications, double uterus, pregnancy in the rudimentary horn of the uterus, torsion of tube complicating labor, pregnancy following the successful repair of vesicocervical fistula, eclampsia, abruptio placentae, and fibroids complicating labor. There were fourteen of these unusual indications.

EUGENE S. AUER.

De Guchteneere, Lahaye, and Foulon: Cesarean Section as a Method of Therapy to Maintain the Circulation of the Cord, Bruxelles-méd. 15: 611, 1935.

The clinical picture of hypertonicity of the parturient uterus, in the absence of any obstacle in the pelvis, and with signs of fetal distress ought to make one think of obstructed circulation of cord vessels. This condition can be relieved only by cesarean section. It occurs more often in the young girl than in the multipara.

J. THORNWELL WITHERSPOON.

Bud, G.: Cesarean Section in the Long Axis, Monatschr. f. Geburtsh. u. Gynäk. 98: 210, 1934.

When a cervical cesarean section is performed, the incision in the lower uterine segment is generally made vertically. However, since in most cases the uterus is rotated to the right, this vertical incision, after the child has been removed from the uterus, runs obliquely toward the left tubal corner. Hence the author makes the incision of the lower uterine segment obliquely directed to the right tubal corner. After the child has been removed this incision then runs vertically.

J. P. GREENHILL.

Fleischer, A. J., and Kushner, J. I.: Experiences With the Latzko Cesarean Section, Surg. Gynec. Obst. 62: 238, 1936.

The Latzko operation is a valuable adjuvant in the armamentarium of every obstetrician. It should not be used promiscuously, but rather is indicated in all cases which cannot be delivered by the vaginal route when there is a temperature indicative of a potential infection and also in patients with normal temperatures, who have been repeatedly examined vaginally or when membranes have been ruptured for a long time.

The operation does entail some technical difficulties which can be overcome by any obstetrician with a sound surgical background and training. It is not a panacea for all frankly infected cases. DeLee's dictum is very appropriate: "Laparotomelotomy for all but those where infection is suspected, then Latzko's operation, Porro, or craniotomy."

WM. C. HENSKE.

Riddell, James: Lower Segment Caesarean Section, Brit. M. J. 1: 792, 1936.

The author points to the advantages of the low cervical cesarean section in contrast to that of the classical operation. A trial of labor is possible; the operation can be performed prior to or after the onset of labor; no haste is required during the operation; the contractile part of the corpus is not invaded; bleeding is less and,

Orrul, Michale: Placental Insertion in the Mechanism of the Rupture of the Uterus Corresponding to Cesarean Section Scar, *Clin. obstet.* 15: 569, 1936.

The author describes a case of twin pregnancy with spontaneous rupture of the uterus in the seventh month. He found placental insertion to have gone deeper into the scar than ordinarily found.

In a second case he reports that the placenta was completely developed into the scar tissue. The rupture of the uterus in this case was complete.

The author emphasizes the predisposing factor created by placental insertion on scar tissue of the uterus. He concludes that the excessive distention of the uterus due to multiple pregnancy is a further predisposing factor for rupture of a section scar. He believes, as many authors at present do, that a low cervical cesarean section would render placental insertion on scar tissue less likely than a classical section.

AUGUST F. DARO.

Trillat, Paul: The Distant Consequences of the Low Cesarean Section, *La Gynécologie* 33: 743, 1934.

The cervical cesarean section has very few late disturbances and permits the normal development of subsequent pregnancies. Spontaneous labor is possible if the pelvis is sufficiently roomy. However, one should not use any medical oxytocics and should avoid all obstetric maneuvers which require force. Since every woman who has had a cesarean section may develop a rupture of the uterus, all labors after a cesarean section should be conducted in a hospital. However, ruptures of the uterus during pregnancy are rare after the cervical cesarean section. Trillat collected from the literature 39 cases of uterine rupture which have occurred following cervical cesarean section.

J. P. GREENHILL.

Fournier, F., and Estienny, E.: Rupture of a Scar During Labor Following a Cervical Cesarean Section, *Bull. Soc. d'obst. et de gynéc.* 25: 185, 1936.

In 1934 Bonnet was able to collect from the literature 37 cases of rupture of the scar following the low, cervical cesarean section. Fournier and Estienny report an additional case in a woman who had twins. The authors believe the rupture was not due to weakness of the scar but to excessive distention and unusual thinning resulting from the presence of a twin pregnancy. The rupture did not occur until after a number of hours of severe uterine contractions. The authors maintain that a scar in the upper part of the uterus would likewise have ruptured under these conditions.

J. P. GREENHILL.

Andérodias and Péry: Spontaneous Labor in Women Who Previously Had Low Cesarean Sections, *Bull. Soc. d'obst. et de gynéc.* 24: 552, 1935.

The authors report a series of 16 women who had vaginal deliveries after having previously been delivered by low, cervical cesarean sections. The indications for the cesarean sections had been contracted pelvis in 11, anomalies of cervical dilatation in 4, and retroplacental hemorrhage in 1. In 9 of the 16 cases forceps were prophylactically applied when the head was at the outlet but in seven instances delivery was entirely spontaneous.

J. P. GREENHILL.

Voron, Brochier, and Magnin: Parotitis After Low Cesarean Section, *Bull. Soc. d'obst. et de gynéc.* 25: 251, 1936.

The authors report 3 cases of parotitis which occurred soon after cervical cesarean sections. All 3 women had defective teeth, hence the authors believed they present evidence of a buccal origin of parotitis. Since spinal anesthesia was used in 2 cases, there could not have been any injury in the maxillary region. In spite of the large number of cases of parotitis which have occurred after gynecologic operations, only one case could be found following cesarean section in a series of 520 cases of parotitis collected from the literature. In fact, parotitis is rare after labor because in a series of 25,000 labors reported from the Koenigsberg clinic there were only 9 cases of parotitis. The authors' case was the only one they observed after 100 cesarean sections.

J. P. GREENHILL.

Huessy, P.: Our Deaths From Cesarean Section, *Monatsschr. f. Geburtsh. u. Gynäk.* 103: 16, 1936.

In the author's clinic from 1921 to 1935 a total of 810 cesarean sections were performed. In this series there were 28 maternal deaths, an incidence of 3.45 per cent. Mortality in the clean cases was 0.37 per cent, in the unclean cases 1.23 per cent. The actual operative mortality was 1.6 per cent. The author warns that it is best to perform cesarean sections only upon clean cases except where it is absolutely necessary to operate on unclean cases. In clean cases there should be no fetal mortality of viable babies and the maternal death rate should not exceed 1 per cent at the very most. When the results of the mother and child are considered together, cesarean section is superior to vaginal operative deliveries. Cesarean section is not a serious operation when it is properly performed for a proper indication and under the proper conditions. The author recalls that even after spontaneous delivery there is a distinct maternal mortality, especially from embolism which does not occur less frequently than after cesarean section. The author believes that in the interest of the child the indications for cesarean section should be extended.

J. P. GREENHILL.

Lindsay, Douglas: Pathological Results of Cesarean Section, *Lancet* 1: 19, 1934.

To stress the importance of operative complication of cesarean section, the author reports the removal of two urinary bladder calculi, one of which was attached to a silk suture from the old uterine scar. Since the only symptom was menorrhagia, the bladder stones were discovered only by routine pelvic examination. No explanation is offered for the silk suture extending into the bladder. The stones were the size of grapes and were phosphatic.

The author states that menorrhagia, abdominal adhesions or uterine fistulas are the more frequent conditions demanding hysterectomy following cesarean sections. Moreover, it is stated that cesarean section operations are abused as much as are forceps and are undertaken often by unqualified operators. Certain errors predominate in the closure: (a) poor reconstruction of uterine wall, (b) infection from poor technique and improper management of patient, and (c) incorrect use of suture and suture material.

Although silk sutures are important for the first row, it is stressed that they must be buried, interrupted and not heavier than a number 3 catgut. Catgut sutures are used also to approximate the muscle and to fix the visceral peritoneum. In the author's series of nearly 200 operations none required later hysterectomy for complication of the sections.

H. CLOSE HESSELTINE.

Erratum

In the article by John I. Brewer and James E. Fitzgerald entitled "Six Normal and Complete Presomite Human Ova," published in the August issue of the JOURNAL, Fig. 16 was unfortunately omitted. It is published below together with several paragraphs in which its mention occurred.

FITZGERALD OVUM

The specimen was obtained by abdominal hysterectomy. The operation was performed because of multiple large fibromyomas. The patient had a normal thirty-day menstrual cycle, and there was no accurate coital history. The hysterectomy was performed on the thirty-fifth day of the cycle.

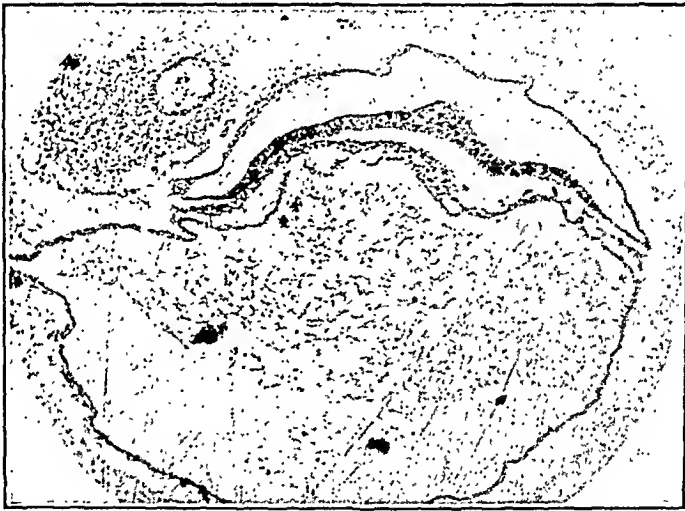


Fig. 16.—The Fitzgerald ovum. This photomicrograph is made of a sagittal section of the embryonic disc. Hensen's node is distinctly elevated. The primitive streak is well defined. The yolk sac is larger than the amnion. In the substance of the body stalk, there is an amniotic duct.

The uterus was as large as a large grapefruit. It contained many subserous and intramural fibroids. The endometrium was without gross pathologic changes. The blastocyst was embedded on the posterior wall of the endometrium in the fundal area and was definitely elevated above the decidual level. The measurements of the ovum are: External chorion 14 by 12 by 9 mm., internal chorion 11 by 10.5 by 5 mm., embryonic disc 1.085 by 0.6 mm., amnion 1.1 by 0.7 mm., and yolk sac 1.3 by 1.2 by 1.4 mm.

There was a primitive streak including Hensen's node (Fig. 16). The blastocyst was covered with branched villi which were as long as 1 mm. The ovum was sectioned in a plane which deviates but slightly from the longitudinal. All sections were saved and arranged serially. A complete reconstruction of the embryo was made through the courtesy of Dr. George Streeter, and drawings of the model were made by James F. Didusch.

Items

American Board of Obstetrics and Gynecology

The next examinations (written and review of case histories) for Group B candidates will be held in various cities of the United States and Canada on Saturday, November 6, 1937 and Saturday, February 5, 1938. Application for admission to these examinations must be filed on an official application form in the office of the Secretary at least sixty days prior to these dates.

The general oral, clinical, and pathological examinations for all candidates (Groups A and B) will be conducted by the entire Board, meeting in San Francisco, California, on June 13 and 14, 1938, immediately prior to the meeting of the American Medical Association.

Application for admission to Group A examinations must be on file in the Secretary's Office before April 1, 1938.

For further information and application blanks address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh (6), Pa.

Mississippi Valley Medical Society

The Mississippi Valley Medical Society offers a cash prize of \$100.00, a gold medal, and a certificate of award for the best unpublished essay on a subject of interest and practical value to the general practitioner of medicine. Entrants must be ethical licensed physicians, residents of the United States and graduates of approved medical schools. The winner will be invited to present his contribution before the next annual meeting of the Mississippi Valley Medical Society (September 28, 29, and 30, 1938), the Society reserving the exclusive right to first publish the essay in its official publication—the Radiologic Review and Mississippi Valley Medical Journal. All contributions shall not exceed 5,000 words, be typewritten in English in manuscript form, submitted in five copies, and must be received not later than May 15, 1938. Further details may be secured from Harold Swanberg, M.D., Secretary, Mississippi Valley Medical Society, 209-224 W. C. U. Building, Quincy, Illinois.

aches, vomiting, and impaired eye sight, and in the international list of "causes of death," eclampsia and albuminuria are even still classed together.

In my opinion this is a mistake; cause and result have here been confused, which is one of the chief reasons why eclampsia is still the illness of theories. In other words, a problem yet unsolved—so far as we can ever speak of a solution to a biologic problem.

We may safely assume at the present time that during pregnancy a number of changes take place in the body under the influence of the metabolic products of the ovum and of the placenta in particular. Further, that these changes, which have come about by selection in the course of millions of years, enable the organism to fulfill its function of propagation, in the widest sense, quite well without harm to the organism itself.

Whenever this is the case, i.e. whenever under the influence of the products of gestation, abnormal reactions occur, we have to do with a morbid condition to which for more than forty years we have applied the term toxemia of pregnancy.

The origin of this term lies in the idea that the kidneys are not able to pass the metabolic products of the child together with those of the mother, whereby first of all the function of the kidneys is impaired, with as consequence the symptoms of uremia, such as headaches, vomiting, etc., and also convulsions.

This idea still holds at the present day, albeit with this difference that it is not the metabolic products of the child, but of the placenta, which are thought to affect the kidneys, and then not even the normal metabolic products of the placenta but special, noxious substances which form under certain circumstances.

This particular toxin, however, has never yet been demonstrated, and in my opinion it is highly improbable that there is any such toxin, if for no other reason than that nearly all gravidas exhibit slight anomalies more or less. This points to there being one general cause of these anomalies, and when we consider that gestation disturbances but very rarely occur in animals, it is obvious that we must look for this cause in the fact that the human being has deviated from nature, i.e. in civilization.

I trust that in the course of this paper I shall be able to convince you that this is indeed the case, and more particularly that it is our custom of salting our food which is on a high degree responsible for these disturbances, especially edema and convulsions.

In how far the hypertension as a rule is partly or wholly a consequence of the consumption of common salt, is not yet certain, for the vascular system is influenced to a high degree by psychic factors, and it is very probable that this accounts in part for the frequent occurrence of hypertension.

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No. 6

Original Communications

THE PREVENTION OF ECLAMPSIA*

PROF. K. DE SNOO, UTRECHT, HOLLAND

BEFORE beginning my lecture, I wish to express my deep sense of indebtedness to your President for his invitation to speak here in your midst, and for the honor he has conferred, through me, upon our Dutch Gynaecological Association.

I assure you that we greatly appreciate the friendly feelings which you have thus shown to our country.

When your President asked me to submit 2 or 3 subjects, I did not hesitate to include among them the prevention of eclampsia, because it is my firm conviction that eclampsia can almost certainly be prevented. For, as I hope to be able to demonstrate, we are not merely in a position to recognize the danger of eclampsia in time by a regular examination of the gravidas, but by means of a diet minus salt, in conjunction, if need be, with narcotics and venesection, we have the almost infallible means of preventing the occurrence of convulsions. And in saying this, I speak from an experience of twenty-five years.

In speaking about eclampsia it is essential to know exactly what we understand by this term.

As the word expresses, this was originally understood to mean a pathologic condition in a pregnant or postpartum woman, characterized by convulsions. Later on, however, the opinion that the convulsions were caused by kidney troubles (nephritis) led to the idea of embracing severe albuminuria, accompanied by uremie symptoms, such as head-

*Read, by invitation, at the Sixty-Second Annual Meeting of the American Gynecological Society, held at Swampscott, Mass., May 31 to June 2, 1937.

NOTE: The Editor accepts no responsibility for the views and statements of authors as published in their "Original Communications."

The results were as follows:

1. All attacks are practically similar and purely epileptiform.
2. They occur at fairly regular intervals.
3. They show a tendency to cease spontaneously without any therapy.
4. They are directly dependent upon the blood pressure, in the sense that we are able, by artificially lowering the blood pressure, to lengthen the intervals between the attacks, or to avoid the attacks entirely.
5. The duration of the eclampsia, the number of the attacks and their severity are not dependent upon whether we have to do with eclampsia antepartum, durantepartum, or postpartum; further, the birth of the child has a favorable effect only if a severe afterbleeding follows with an appreciable lowering of the blood pressure.

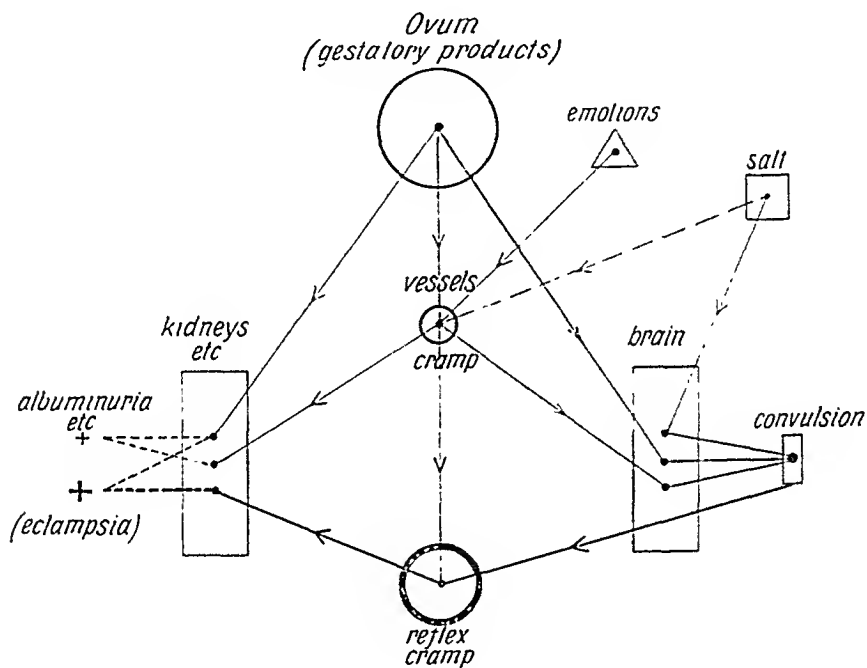


Fig. 1.

6. The course is similar in multiparas and primiparas, in women with normal kidneys and with chronic nephritis.

7. The blood pressure invariably rises immediately after an attack.

We could not, therefore, do other than draw the conclusion that if eclampsia has once made its appearance the attacks are governed by a certain mechanism, which runs, as it were, like clockwork until, after a certain time, on an average twelve hours, it comes to a standstill. And this assumption finds confirmation in a few observations made during the early years when, more than once, a second series of attacks occurred three or four days later, even occasionally followed by a third series. (This was at the time when we were still giving a milk diet. After a saltless diet had been substituted a recurrence never took place, not even in women with intercurrent eclampsia.)

At all events the vascular system plays a large part in the pathogenesis of the anomalies of pregnancy, and it is probable that the last cause of the defective functioning of kidneys and liver, and also of the eclamptic attack, is due to vasomotor cramp and the resulting defective circulation.

It is not the object of this paper, however, to inquire thoroughly into the pathogenesis, since it is the prophylaxis which claims our attention today. I will confine myself to the remark that various observations, for instance, the premature separation of the placenta whereby, just as in eclampsia, some times anuria and even necrosis of the renal cortex may be observed, point to the convulsions as causing reflex vascular constriction. This is the reason for the severe albuminuria in women with eclampsia when the spasms last too long and the tissues are particularly sensitive, as also of the bleeding and the necrosis in the liver.

But this same vascular cramp may also arise gradually, without convulsions, as a direct reaction to the pregnancy. And when this vascular cramp lasts long and is severe, and the tissues are sensitive, the same symptoms may appear as in eclampsia, i.e. eclampsism. And now we understand why we have so long thought that eclampsia was the consequence of the diseased kidneys or liver, whereas it is, on the contrary, just the liver and kidneys which become impaired by convulsions. Fig. 1 gives a survey of this theory.

There are several facts which tend to show this.

1. There is no parallelism between the severity of the toxemia and the danger of eclampsia.

In the majority of cases eclampsia occurs even in women who to all appearances had been healthy, and reversely, the number of women with serious toxemia who get eclampsia, irrespective of the therapy, is small.

2. Is the urea percentage in the blood at the moment of the outbreak of eclampsia generally normal, but rises not infrequently some time after the attacks have ceased, while the prognosis of the gestatory albuminuria is independent of whether convulsions have occurred or not?

3. As regards the liver function, we often find that the bilirubin percentage of the blood does not rise until after the attacks.

But this is not all.

After I had studied successively the relation between edema and eclampsia, between albuminuria (and the kidney function) and eclampsia, and between hypertension and eclampsia, I studied the attacks themselves, in a long series of cases (136) (viz. the number, the length of the intervals, the influence of the parturition, of the loss of blood, of narcotics, etc.) particularly in connection with the blood pressure which, for this purpose, was measured every five minutes.

TABLE I

ECLAMPSIA BREAKS OUT AFTER ADMISSION												
CASES OF TOXEMIA	HOURS			DAYS			WEEKS					
	0-6	6-12	12-24	1-2	2-3	3-4	4-7	1-2	2-3			
Milk diet (Rotterdam)												
1907	61	1	1	1			2					
1908	59	1	1	1		1	1					
1909	70	1										
1910	65		1									
1911	94	1					1					
5 years	349	4	1	2	2	1	4					14
Salt-free diet (Rotterdam)												
1912	62	2										
1913	69	1	1									
1914	65											
1915	58		1									
1916	82		2	1								
1917	130				1							
1918	70	1									1	
1919	59	1			2							
1920	101	1										
1921	62	3			2							
1922	77		1									
1923	91											
1924	113		1	1								
1925	125				1							
56							1					
15 y. 1926	1220	9	5	3	5	1	1				1	25
Salt-free diet (Utrecht)												
1927	62											
1928	75					1	1				1	
1929	70		1									
1930	73					1						
1931	80					1						
1932	62	1										
1933	56	2										
1934	76	1										
1935	120	2	2									
1936	142				1							
10 years	816	6	3		1	3	1				1	15

But, if we have to assume a certain mechanism in the occurrence of the attacks, this implies that this mechanism is regulated, and that there must be some center from which such a regulation takes place. And then it is not difficult to see that eclampsia cannot merely be the consequence of irritation of the cortex cerebri, but of irritation of that center, whereby outbursts result, i.e. the convulsions. And in how far it may come to outbursts in a particular case thus depends on the one hand upon the excitability of this center, and on the other hand upon the presence of special irritants to which the hypothetical center is susceptible (Fig. 1).

In thus presenting the character of the convulsions, it will be clear how incorrect it is to speak of eclampsia and toxemia in one breath, and that we must regard the eclamptic attack as a separate entity of pregnancy, the consequences of which, owing to reflex vascular cramp, are qualitatively the same as toxemia proper, though generally *quantitatively much more severe*, and this is not affected one jot by the fact that in general already prior to the fits there were more or less clear symptoms of toxemia. So it becomes comprehensible why in many cases eclampsia occurs in women who to all appearances are healthy, while, on the other hand, it does not appear by any means in all women who suffer from severe toxemia.

As you will see presently, of about 2,400 women who in the course of time were admitted in the clinic suffering from toxemia, only 54 had eclampsia. And although the measures we took undoubtedly prevented many an attack of eclampsia, yet we may safely assume that of that large number, the greater majority would never have had eclampsia, even without any treatment.

On the other hand, among the women admitted with eclampsia were many who but shortly before had neither albuminuria, nor headache, nor any other pronounced symptoms, and even two normal patients admitted for delivery had eclampsia who not only had no albuminuria or hypertension but no edema either.

Regarded in the light of the theory of a "cramp-center" all this will be clear.

There is thus every reason to keep toxemia and eclampsia distinct, and to understand by the prophylaxis for eclampsia only the prophylaxis for convulsions, that is, of the explosions of the cramp-center.

It has appeared that women who have a normal blood pressure practically never get eclampsia, neither do women who have lived for two or three days on water, or on a diet minus salt. This is of the greatest importance in the practice of the prophylaxis, because in measuring the blood pressure we possess the means of early diagnosing the danger of eclampsia, and on the other hand, as I will show you, by means of water and a salt-free diet, respectively, of averting that danger with almost absolute certainty. I will show you this on this table, which gives a survey of my experience during 30 years (Table I).

catheter. The child is then usually born within twenty-four hours, and since the therapy of a saltless diet plus water has been employed, eclampsia has not once occurred in a series of more than 100 patients who had labor induced and who had been so treated for not less than two days previously.

This is the second proof of the importance of the salt-free diet. A third proof is the fact that in women with intercurrent eclampsia, i.e. in women whose attacks had ceased before labor began, a second or even a third series of attacks never occurred, as used to happen repeatedly in the first periods, with a milk diet.

A diet minus salt is therefore much to be preferred to a milk diet (although by this I do not mean to say that a milk diet may not be useful). Milk, however, contains 1.7 gr. of NaCl per liter, so that in the consumption of 4 liters per day about 7 gr. of salt are consumed, against only 1 or 2 gr. with a salt-free diet. Apparently this quantity is still too high in some cases.

In food salted in the usual way we consume 15 or 20 gr. of NaCl per day. And herein lies the last cause of eclampsia. We salt our food to make it palatable. And it is this salt that we must up to a point regard as the eclampsia toxin; not what is formed in the body, but what enters from without. If, therefore, all gravidas were to be put on a salt-free diet, there would be practically an end of eclampsia.

This, however, is not necessary, for, as I mentioned above, retention of salt is not the sole condition for the attacks of eclampsia. An increased blood pressure is also an essential, and experience has taught that this can generally be detected betimes, even in out-patients, as I shall presently show you.

But first, a few words respecting the edema and the influence of abstinence from salt upon the composition of the blood. No fewer than 70 per cent of gravidas suffer from edema, and of the others 30 per cent have a preliminary edema, as is evinced by their losing weight, post-partum. If, however, the gravidas are fed upon a salt-free diet there is no edema, nor do they lose weight after the confinement, so that the cause of the edema must be looked for in our custom of salting our food to make it palatable. Meat, butter, cheese, and potatoes are prepared with salt, and the baker uses large quantities of salt in the baking of bread, biscuits, and all kinds of cake. In this way we consume on an average of about 15 gr. of salt extra, and can assimilate this without discomfort.

During gestation, however, the tolerance of NaCl diminishes as pregnancy proceeds, and the tissues retain the salt, which causes water retention, with ensuing edema. But the salt percentage in the blood remains practically unchanged. By abstaining from salt, the tissues set the surplus-salt free, so that the kidneys are able to pass it, and simultaneously the edema decreases or disappears.

In the first period, 1907 to 1911, I began with a milk diet and gradually changed the milk for salt-free food. In the second and third periods the patient was given exclusively a salt-free diet, with 1 or 2 liters of water extra. Most patients were admitted with the diagnosis of impending eclampsia or with hypertension and albuminuria. However, not more than 54 had eclampsia, and as you see almost the same frequency on milk as on a salt-free diet which, in my opinion, goes to prove that in a great number there was no danger of eclampsia at all. Still, in others this would have been the case, but now you see that of 348 women on a milk-diet, 5 after three days developed eclampsia as against only 4 of 2,000 women who had been given a salt-free diet, and in each of these 4 cases it can be demonstrated that mistakes had been made with the diet.

Moreover, these women had but 1 or 2 attacks, so that the treatment had not been quite unavailing.

This, in my opinion, establishes the important significance of the salt-free diet.

But to obtain good results, the diet must be carefully prescribed, and strictly adhered to and controlled. This frequently involves some difficulty, either because the physician or the nurse is not wholly convinced of its infallibility, or because the patients, consciously or unconsciously, make mistakes. In this respect it may be worth mentioning that when I took over the management of the Clinie at Utrecht with the old nursing staff, it took three years of hard work before I had banished eclampsia.

This use of this word is justified by the fact that in the last seven years not a single case of eclampsia has occurred in my Clinie later than two days after the patient had been admitted.

The easiest method of determining the NaCl in the urine is with the chlorometer of Strauss, with a graduated test tube.*

As a rule the edema disappears or diminishes with a salt-free diet, though by no means invariably; very occasionally it even grows worse, as the scales quickly show.

After two days however, and that is the important thing, there is no need to fear attacks of convulsions, not even when the symptoms of toxemia increase and the women become seriously ill.

In such cases I do not perform a cesarean section, as has been the practice of recent years, but I induce labor by means of a condom

*The apparatus is filled up to stripe A with the solution of Martius Lüttke, which contains a certain quantity of nitrate of silver and sulphate of iron. (a. 17 gr. nitratis argentii are to be dissolved in 200 or 400 c.c. aqua destillata and 500 gr. acidum nitricum added. b. 40 gr. sulfas ferrius are to be boiled in 100 c.c. water, until it is completely dissolved; then cooled and filtered. a. and b. are to be joined and supplied with aqua dest. up to 1 liter.) Then it is filled up to stripe U with the urine to be examined and shaken.

The AgCl will then be precipitated and there will remain a surplus of nitrate of silver, which is titrated back again with a solution of sulphocyanate ammonium. (3.9 gr. sulfocyanetum ammonicum on 1 L. aqua dest.)

As soon as the AgNO₃ is fixed by the sulphocyanate ammonium, it colors red, the ferrous sulphate acting as indicator.

The quantity of NaCl per liter in the urine is indicated by the number at the stripe to which the fluid reaches.

This was the case, thirty years ago, of a sixteen-year-old girl who was admitted with severe edema and albuminuria. On a milk diet the edema grew worse; the diuresis was moderate, and the urine contained fairly little salt. After four days she developed an eclamptic attack which did not cause much change in the functioning of the kidneys. Four days later labor was induced and a mole was expelled. Immediately the diuresis increased, already the first day almost 5 liters, and the NaCl percentage also rose so much that in the first week nearly $\frac{1}{2}$ Kilo of salt was passed (Fig. 2).

The increase in the diuresis was so rapid (and this can be repeatedly observed) that the kidneys could not possibly have recovered in so short a time, and thus the edema cannot have been the consequence of the impaired kidney function but must be ascribed to the greater *affinity* for salt of the tissues by reason of the circulating gestatory products.

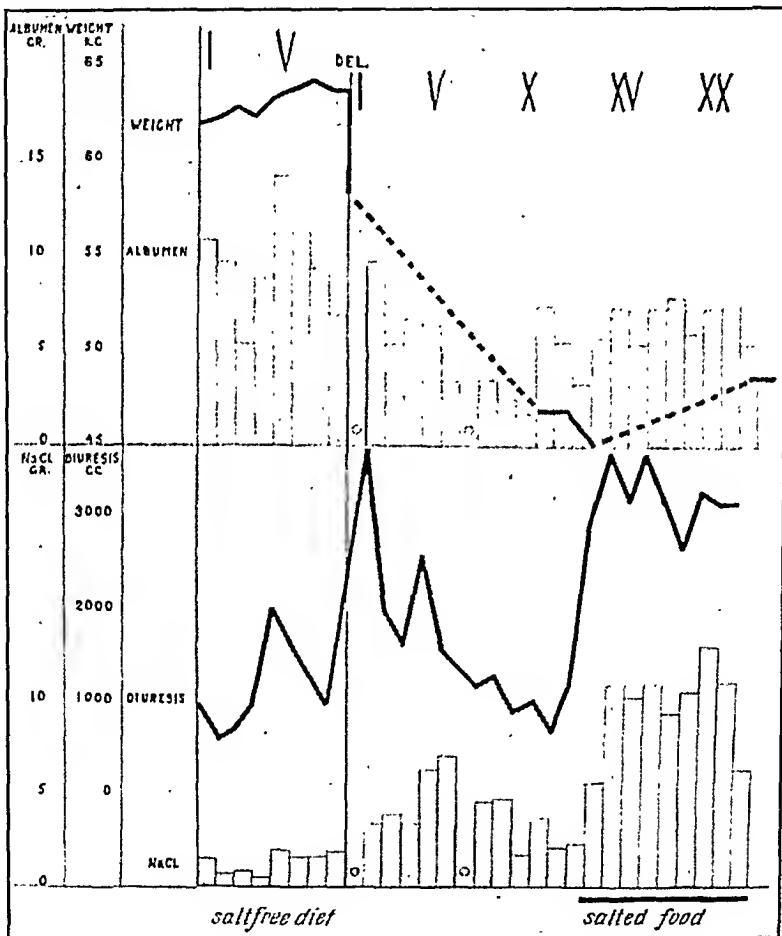


Fig. 2.

That this is actually the case has been proved by examining the influence of a salt-free diet upon the composition of the blood.

For many years, we have examined the Na, K and Ca content of the blood of all our patients with toxemia and eclampsia, in many cases at different times, on admittance and before and after parturition. We have studied the influence of a water and a salt-free diet, respectively, and compared normal nonpregnant women, with normal gravidas, gravidas with toxemia, nephritis and eclampsia.

Thus, by means of a salt-free diet we were able in many cases to cure the edema completely before parturition, as is best seen by the fact, that the patient does not loose weight postpartum anymore.

In other cases we did not attain a complete cure, and even occasionally the edema increased, notwithstanding the diet, but even in these cases there is after two days no danger of eclampsia.

CASE 1.—Para i, twenty-five years of age, is admitted with strong albuminuria (10 per cent) and considerable edema. Notwithstanding salt-free diet the weight increased, but no eclampsia occurred. Three weeks anteterminum a living child was born spontaneously, after which immediately a large diuresis began and the edema disappeared. As Fig. 2 shows, the weight increased in childbed with 13 Kg.; after taking salted food again, the weight increased with 2 Kg. One sees in the figure, how the NaCl excretion after parturition was much larger than before parturition.

After parturition, the tissues set the salt free, and it is passed with the urine. This is the reason for the increased diuresis generally immediately postpartum, and for the large quantities of salt then passed. You will permit me to illustrate this with an example from my early practice, which made a great impression on me and influenced the direction which my eclampsia researches have taken (Table II).

TABLE II

DATE	QUAN- TITY	SPEC. GRAV.	ALB. 0/00	ALB. IN 24 HR.	NaCl PER L.	NaCl IN 24 HR.	REMARKS	FOOD
1907 Nov.								
19	670	1023	12.0	8.4				3 liter milk
20	1040	1010	3.5	3.64	7.1	7.38		3 liter milk
21	1240	1014	6.0	7.44	5.0	6.2		4 liter milk
22	550	1037	12.0	6.6	2.0	1.1	Eclampsia	3 liter milk
23	890	1017	5.0	4.45	2.3	3.05		4 liter milk
24	2760	1008	2.0	5.52	2.4	6.62		5 liter milk
25	1300	1010	2.0	2.6	2.5	3.25		4 liter milk
26	1050	1011	4.0	4.2	4.9	5.14	Abortus provocatus	1½ liter milk
27	4870	1010	0.3	1.46	7.0	34.09		3½ liter milk
28	4610	1007	0.5	2.3	8.2	37.8		5 liter milk
29	3460	1011	1.0	3.46	5.6	19.37		4 liter milk
30	2700	1008	1.0	2.7	5.0	13.5		5 liter milk
Dec.								
1	2600	1010	0.5	1.3	8.2	21.35		4 liter milk
2	2450	1010	0.5	1.22	6.0	14.7		4 liter milk
3	2860	1009	0.75	2.14	6.8	18.04		5 liter milk
4	2500	1010	0.3	0.75	9.5	23.7		4 liter milk
5	2280	1011	0.3	0.68	7.4	16.87		3 liter milk
6	2780	1011	0.25	0.69	8.3	23.07		5 liter milk
7	2430	1010	0.2	0.48	8.2	19.92		5 liter milk
8	2920	1009	0.2	0.58	8.8	25.69		5 liter milk
9	2940	1010	Trace		11.8	34.69		5 liter milk
10	2660	1009	Trace		7.3	19.42		5 liter milk
11	3190	1007	Trace		4.6	14.67		5 liter milk
12	2760	1009	Trace		5.2	14.04		5 liter milk
13	3010	1010	Trace		3.8	11.43		5 liter milk
14	1740	1011	None		2.9	5.04		5 liter milk
15	2080	1013	None		2.7	5.61		5 liter milk

which an accumulation of salt arises, which is the more considerable as the affinity is more intense or the quantity of salt in the blood higher.

It may be that especially the Na combines with the water thereby causing edema, and according to Zangemeister and numerous other authorities, this edema increases the brain pressure and thereby causes convulsions. These researchers even hold edema to be primary and salt retention to be secondary, and therefore lay the chief stress upon the abstinence from liquid. Yet Zangemeister also gave his patients a salt-

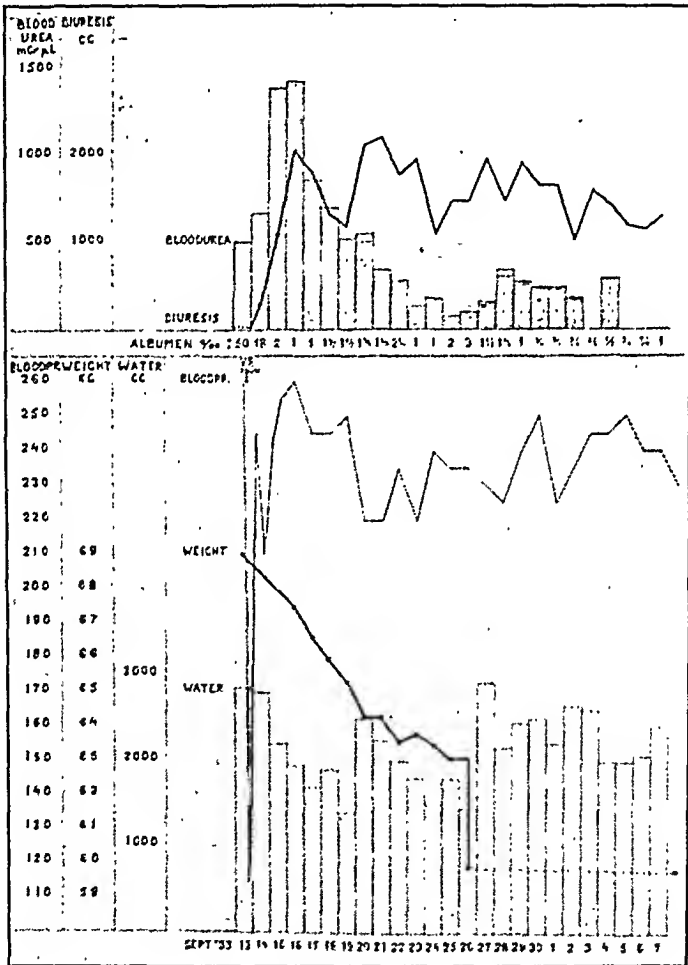


Fig. 4.

free diet, or rather a diet poor in salt, though not on account of the salt itself, but to enable his patients to refrain from drinking. Moreover they attached great value to limiting the fats and albumin.

My patients, on the contrary, may have anything they like, except milk, but all without salt and with an additional liter or two of water. Table I shows most clearly that this water has no ill effects. On the contrary, it is beneficial; severe cases of toxemia even with anuria can be cured thereby, as the following example will show.

Fig. 4 shows the quantities of water, the diuresis, the weight and quantity of salt excreted in a primipara, who on admission had extensive edema, a high blood

As a matter of fact the number of investigations amount to about 1,000, all carried out in the same way and by the same person.

These researches have shown:

1. That there is practically no difference between the Na content of the blood, in gravidas and nongravidas and in normal and toxemic women with normally salted food.

2. That on a salt-free diet invariably the Na content diminishes, as well in normal gravidas as in toxemic ones, on an average of 5 per cent (from 333 mg. to 317 mg.) as is seen in Fig. 3, regarding 100 cases of toxemia, where there is a considerable divergency in the figures of the sodium content of the blood in salted and salt-free food.

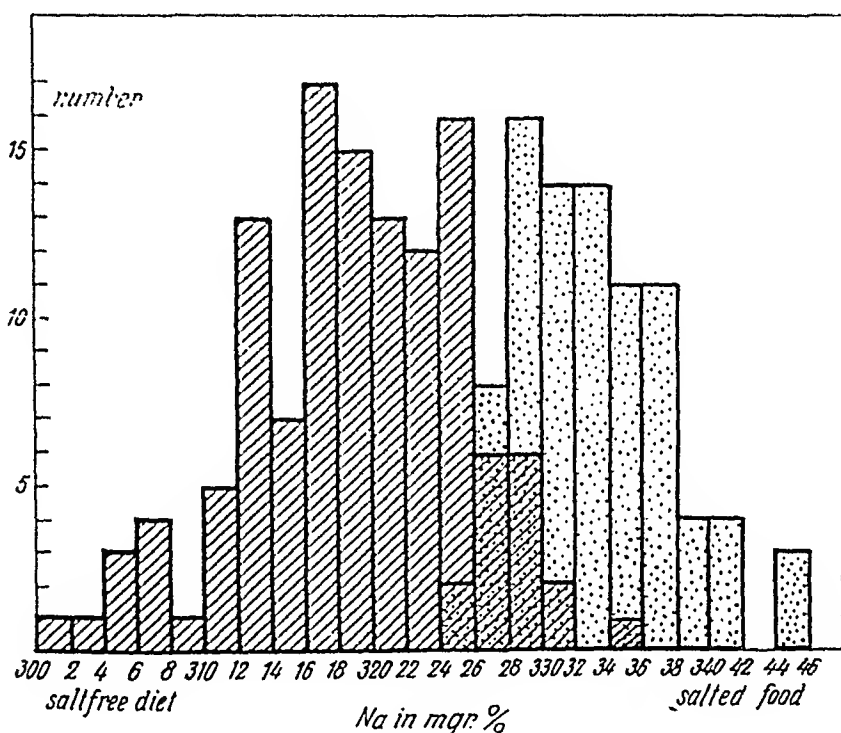


Fig. 3.

3. That in eclampsia the Na content in most cases is approximately normal, but in other cases abnormally high, until 370 mg. and more.

4. That the influence of the salt-free diet on the chlorine content is about the same, as on the Na content.

The calcium and potassium content on the contrary do not change.

The fall of the NaCl percentage is about the same in normal and in toxemic gravidas, in gravidas with and without edema, and is even independent of the fact, whether the edema disappears after water or salt-free diet or not, of whether eclampsia has preceded or not.

It is of great importance, that after parturition in all women the NaCl content of the blood serum temporarily increases, notwithstanding the continuation of the salt-free diet; on an average by 5 mg.

Apparently the tissues retain the salt under influence of the gestatory products; in pregnancy they get a heightened affinity for salt, through

During the first years they were seen on an average of 3 times; in the last year on an average of 5 times. This shows the growing confidence of the public.

About 25 per cent were put upon a salt-free diet, a large quantity.

A specification of this figure for the year 1936 follows here:

FREQUENCY OF SALT-FREE DIET

<i>Utrecht:</i>	
Number of inhabitants	±175,000
Number of births, 1936	3,335 = 19%
<i>Department of University:</i>	
Number of births	2,149
Clinical confinements	256
Home confinements	1,873
<i>Salt-free diet</i>	562 = 26.1%
Indications:	
Edema only	251
Edema + hypertension	124
Edema + hypertension + albuminuria	23
Hypertension only	133
Hypertension + albuminuria	14
Albuminuria only	6
Prophylaxis	10
Epilepsy	1
	562

It should be noted that many women often exhibit hypertension on the first examination, a symptom, which is purely psychogenic. To make sure as far as possible that the diet is being strictly kept, the women get a diet-list and at their next visit, a week later or even earlier, they must bring a urine specimen, which is then examined for the salt percentage, as I have already described.

The delivery, whether in or outside the Clinie, is, as a rule, strictly expectant, i.e. within normal limits it is allowed to proceed without interference; and without narcotics. The total number of registered confinements in these ten years was about 20,000, clinical births included.

Forty-five women died after registration, 10 before birth, 35 after birth. There were 27 puerperal deaths:

Sepsis	9
Embolism	5
Placenta previa	6
Premature separation of the placenta	2
Hemorrhage postpartum	3
Apoplexia	1
Anesthesia	1

Nonpuerperal deaths—10

Tuberculosis	6
Pneumonia	4
Hematemesis	1
Appendicitis	1
Coma diabeticum	1
Paralysis cordis	2
Full-term ectopic pregnancy (laparotomy)	1
Unknown cause, antepartum	2

pressure (230), marked albuminuria (50 per cent), vomiting, and epigastric pains. To prevent the outbreak of convulsions a vena section of 500 gm. is performed and morphine given. The diuresis had almost stopped. The patient is given much water, no salt. The diuresis increases first slowly, then more rapidly, whereupon the weight decreases and the edema disappears, but the blood pressure remains high. No convulsions occur. You will observe the great quantities of water used, and yet the deep fall of the weight. In the first days the urea content of the blood augmented from 600 until about 1500.

It is my firm belief, therefore, that there can be no longer any doubt that the salt is the culprit and that it is to blame not merely for the eclampsia but partly also for the toxemia.

It would be well if the women were to be forbidden the use of salt in the second half of their pregnancy. There would then be far fewer cases of serious toxemia, and it would practically put an end to eclampsia.

Such a measure, however, as was remarked above, is not required, because we are able to detect the danger of eclampsia in time, not only in the hospitals but also in the ordinary practice, which implies that the prophylaxis of eclampsia has become simply a matter of organization, in other words, of prenatal care.

And herewith I come to the practical part of the prophylaxis of eclampsia. This is not such a simple question as it appears at the first glance, for it demands a vast amount of work which, and that is the drawback to all prophylaxis, is not adequately appreciated.

Many women, in my department too, evade the control, and many others do not keep strictly to the prescribed orders. The consequence is that the results are not what they might be. But if we are not disheartened by an occasional case of eclampsia, but after each fresh case take new and more stringent measures, the results will be by no means unsatisfactory, as is seen in my Obstetrical Department at Utrecht. You will allow me, therefore, to give you a short survey of this work, with annexed prenatal care together with the results that have been attained in the last ten years.

In Utrecht, a town with $\pm 175,000$ inhabitants, about 3,000 children are born every year, of whom $\pm 2,000$ come under my department.

Of these about 250 are admitted in the Clinic, the others are delivered at home with the aid of students, under control of one of the assistant doctors.

When the expectant mother reports herself, which as a rule is in the seventh month, she is registered and weighed, the blood pressure measured, the urine examined, the size of the uterus and the position of the child determined and, if necessary, the pelvis is examined internally. When there are no anomalies, the women are bidden to return every fortnight for control; in other cases earlier, and, if need be, they are treated at home, or admitted to the Clinic.

When indeed the salt has the signification which I believe it has, it merely depends upon the organization of the prenatal care and in particular on the cooperation of the public how many cases of eclampsia still will occur.

In Holland, great attention has been paid to the prenatal care for more than forty years. As can be readily understood, the results are not equally favorable everywhere.

Of 175,000 births, there were 64 deaths from eclampsia and albuminuria in 1934, and in 1935, 75.

From figures furnished me by the Statistieal Bureau, I find that of these 75, 54 died from eclampsia, namely one in about 3,000 deliveries.

This low mortality is especially due to the help of the midwives in prenatal care. This they have allowed by law to carry on for some years now. For more than forty years the probationer-midwives at the Training Schools, have been taught to examine the urine, every fortnight, and for twenty years they have also been instructed to determine the blood pressure, and many do this conscientiously in their practice. Further, a vigorous propaganda for prenatal care has been carried on, verbally and in writing, and in particular at the Classes for Mothers, which were instituted in 1912, and have been given for many years now in every town and every village by the "Green Cross" organization.

Besides the individual prenatal care, which extends to the Lying-In Hospitals and Midwifery Wards of the Hospitals in the cities, the need of organization of the prenatal care has made itself felt in the country especially, and an Association has been formed for prenatal care as a subdepartment of the Netherlands Association for Infant Welfare, with the support and cooperation of the State.

The Association organizes and controls the prenatal care over the whole country. The leading principle is, that every woman is controlled as much as possible by her own doctor or midwife.

This Association is drawing the reins tighter and tighter. And this is necessary, for still there are many women who evade our control. But fortunately we are so far that there is now no doctor or midwife who would not be ashamed to have any of their patients develop eclampsia.

We have confidence, therefore, that the figure for eclampsia may still be reduced, and this will be due in large measure to our blood pressure control, which hardly ever fails to give timely warning, and to the salt-free diet, which enables us with almost complete certainty to ward off the impending danger.

These two facts in my opinion dominate the prevention of eclampsia, and I venture to recommend them to your careful attention.

DISCUSSION

DR. WILLIAM J. DIECKMANN, CHICAGO, ILL.—Dr. De Snoo has stressed the importance of chloride retention, hypertension, the danger of fits because of their

There were 27 puerperal deaths, but, what is of the greatest importance, *not one patient died of eclampsia*, or of toxemia.

Yet 21 of the 20,000 women did get eclampsia, and it is essential to inquire further into these cases.

A. It appears, then, that of these 21 women 9 are primiparas, and 12 multiparas, which is a different proportion to the usual one. There is little doubt that this will be because the primiparas submit to be controlled much better than do the multiparas.

B. Two women had eclampsia in whom shortly before not a single anomaly was to be found. In our ward practice, too, we met with 2 such cases.

Three times the eclampsia occurred the day after the woman was registered: once in the twenty-fifth week, once in the thirty-third week, and once in the thirty-ninth week, all three shortly after being admitted to the Clinic, one almost immediately after admission, while still in the bathroom.

These women were thus too late.

Three women failed to return after having been prescribed a diet. Eleven had been controlled regularly, but had not adhered strictly to the diet, and,

Twice the necessary prescriptions were not given, notwithstanding serious anomalies.

C. Further it appeared, that the 2 women, who had evinced no anomalies, had 5 and 8 attacks.

The women who failed to return had on an average of 5 attacks.

The women who had not kept their diet strictly, had only 3 to 5 attacks. All these women have recovered, but on the other hand by the same treatment, from 60 other women, who were admitted with eclampsia, 13 died. It is evident, that the prognosis of eclampsia does not depend only upon the manner of treatment, conservative or active, but in a high degree upon the use of more or less salt in the preceding days. This would perhaps explain the great difference in the mortality in different countries, especially the beautiful results of Stroganoff, whose mortality, in Leningrad is only 2.9 per cent, a mortality which, I think, nobody else can boast. To make sure it is necessary to know the frequency and severity of eclampsia in the different countries in relation to the welfare.

As you know the frequency of eclampsia in Germany during the war was very low, and also in Rotterdam, the frequency had sunk in 1918 to almost a third.

In my opinion this is to a great degree due to the small use of salt as an immediate consequence of the shortage of food.

In my report of geographic eclampsia for the International Gynaecological Congress in Amsterdam, 1938, I especially will pay attention to this undoubtedly important point.

TABLE II. C. W. (THIRTY-EIGHT YEARS OLD, GRAVIDA VIII, PARA VII, TWIN PREGNANCY AT TERM, POLYHYDRAMNIOS)

	URINE: AVERAGE PER 24 HOURS			B. P. MM. Hg.	WT. KILO	SERUM PROTEIN GM. %
	VOLUME C.C.	NaCl				
		GM.	GM. %			
2/14				160/ 60	88	Admitted to the hospital 5.3 Delivery 4.8 5.5
2/28				114/ 60	89	
4/18	140	1.0	0.72	172/ 95	109	
4/19	400	2.7	0.67	215/118		
5 days	4,450	7.4	0.18	185/105		
11 days	3,036	19.8	0.66	160/ 95		
3 days	2,600	2.6	0.10	145/ 90		
5/1				135/ 90	68	
6/6				125/ 75	70	

Table II lists essential data from a patient who had no convulsions. The close relationship between weight gain, edema, hypertension, and proteinuria is evident. The marked excretion of chloride after delivery with the patient on a salt-poor diet is indicative of the retention which had occurred previously. As the edema decreased, the blood pressure returned to normal and other abnormal symptoms and signs disappeared. We have noted that improvement does not occur before delivery and not always then, unless the chloride intake is reduced to such a degree and the restriction maintained long enough in order that the total excretion in the urine is less than 3.0 gm. as NaCl.

I have always looked upon the convulsion as being only one sign in the disease, eclampsia, and have felt in general that, as long as the patient is able to respond to the abnormal condition by having convulsions, the prognosis is more favorable than if coma, hyperpyrexia, anuria, etc., develop without convulsions.

If Dr. De Snoo is correct in attributing the importance which he does to the hypertension and a theoretical cramp center, then the higher the blood pressure, the more serious the eclampsia. This has not been our experience. I prefer an eclamptic patient with a blood pressure of 200/170 to one with a blood pressure of 160/130. One of our fatal cases was a patient who had a maximum systolic pressure of 128.

At the Chicago Lying-In Hospital in a period of five years and seven months, during which there were 14,864 deliveries, 52 patients had eclampsia, an incidence of 0.346 per cent. Thirty-two of these eclampsias occurred before delivery and the remainder occurred postpartum.

TABLE III

	PRENATAL SUPERVISION		FAULT		
	CARE	NO CARE	DOCTOR	PATIENT	NO ONE
Our clinic	23	6	18	10	1
Other clinics	4	2	4	2	
Private patients	13	4	16	1	
Total	40	12	38	13	1

Prenatal Care.—In Table III, data are given as to the amount of prenatal care, and I have attempted to assign the fault of eclampsia to either doctor or patient with the result that in only one case was no one found responsible for the eclampsia and the resultant death. Such reasoning is fallacious, because after the patient has had eclampsia, it is easy to state that some other procedure might have prevented the disease or saved her life. It is interesting that 38 patients were seen one week or more before the delivery, and the doctor was apparently at fault in not preventing eclampsia in these patients. It is also interesting that the first symptom

associated vascular spasm, and the normal kidney. He also postulates a cramp center. He states very definitely and proves with statistics that they have been unable to prevent toxemia but can prevent eclampsia in the majority of patients. I agree with him in most of these points but differ in the importance which he attributes to the *fit per se* and the degree of hypertension.

It has been demonstrated experimentally that if the brain is first dried out by means of a hypertonic solution it will require a larger amount of the stimulating substance, for example, absinthe, to produce convulsions than with the normal brain. I believe that one can account for the convulsions of true eclampsia on physico-chemical changes between the blood and the fluid in the tissue spaces.*† Where the patient has gained excessively in weight but shows no edema, convulsions rarely occur. Occasionally these patients, within a period of a few hours, will show evidence of very marked pitting edema. In other words, the water which has been bound has for some reason become free, and it is in these patients that convulsions are most likely to occur and also symptoms of cardiac failure as evidenced by pulmonary edema, cyanosis, and tachycardia.

Patients with essential hypertension may also have convulsions which are presumably due to changes in the arterioles and capillaries. These fits, if they occur in the pregnant woman, cannot be differentiated from those of eclampsia. It seems to me that some of the apparent contradictory results with various therapeutic procedures for treating eclampsia can be attributed to these two different etiologic causes. True eclampsia due to the pregnancy and characterized by a wet brain, marked alterations in blood and plasma volume and other abnormal physiologic changes is not so amenable to treatment and is cured as a rule only by relatively early delivery.

The convulsions due to a hypertensive encephalopathy are not materially affected by the pregnancy, although the latter condition may favor their occurrence and are readily controlled by hypnotics. Since the pregnancy is not the cause, early delivery is not so important. We do not know what eclampsia is and, therefore, cannot at present differentiate these two conditions during the acute attack but believe such a possibility should be kept in mind.

We reported before this Society in 1929 data on the retention and excretion of sodium chloride by the preeclamptic and eclamptic patient. In 25 patients with eclampsia,‡§ the chloride concentration of the urine on admission ranged from 0.002 to 0.41 gm. per cent, with an average of 0.185. Data from two eclamptic patients who were discussed in the previous report are presented in Table I. W. P. showed almost no chloride excretion before delivery, although on a salt-poor diet. The maximum diuresis in both patients occurred when the serum protein concentrations were at their minimum.

TABLE I

PATIENT	TIME	WT. LOSS IN 3 WK. PERIOD KILO	SERUM PROTEIN GM. %	URINE: AVERAGE PER 24 HOURS			
				NO. OF DAYS	VOLUME C.C.	NaCl	
						GM.	CONC. GM. %
W. P.	Antepartum		5.6	2	1,000	0.12	0.008
	Postpartum	20	4.3	3	4,700	13.6	0.31
M. W.	Antepartum		6.8				
	Postpartum	50	4.9	3	4,816	20.77	0.43

*Dieckmann, Wm. J.: AM. J. OBST. & GYNEC. 32: 927, 1936.

†*Idem. Ibid.* 26: 543, 1933.

‡*Idem.* AM. J. OBST. & GYNEC. 29: 472, 1935.

§Schwarz, O. H., and Dieckmann, Wm. J.: *Ibid.* 18: 515, 1929.

TABLE IV

HOSPITAL DELIVERIES	NUMBER OF DELIVERIES	ECLAMPSIA		NONCONVULSIVE TOXEMIA	
		INCIDENCE	MORTALITY	INCIDENCE	MORTALITY
		% 1	..%	%	% 1
Chicago Lying-In Hospital	13,735	0.36	6.0	7.28	0.30
Collective—U. S.	254,564	0.583	13.06 (194)	4.41	1.68 (156)
Collective Range—U. S.		0.6-7.2	0-50.00	0.2-29.6	0-13.0

The approximately equal number of deaths from eclampsia and nonconvulsive toxemia is also of interest. These figures indicate the need for more study of the latter group and earlier recognition of the criteria necessary for interruption of the pregnancy.

These questions can be answered if a sufficiently large number of patients can be studied and treated with the various "treatments." This presupposes cooperation between universities and hospitals. The initiative in such a plan for co-ordinating study of the toxemias of pregnancy should be by the special societies or by one of the large research foundations. The latter is preferable for many reasons.

Dr. De Snoo has mentioned the diet as a factor in the cause of eclampsia. I wish to call attention to our work on nonpregnant dogs.* These animals were fed meat and at the proper time interval were given placental extract intravenously. Over 50 per cent of the animals had hemorrhages and necrosis about the portal spaces of the liver and beneath the capsule. We suggest that this work indicates that protein, especially meat or fish, is contraindicated in patients with pre-eclampsia. It is probably not injurious to pregnant patients with essential hypertension.

In 12 patients, 5, or 40 per cent, gave a history of previous toxemia. Likewise, 5 out of 21, or 22 per cent, had toxemia in subsequent pregnancies. The number of cases is small because in a larger group of nonconvulsive toxemia we find a much greater incidence of toxemia after eclampsia.

The treatment† which we have been using has been described on several occasions and may be summarized as follows:

TREATMENT OF ECLAMPSIA

General: Constant observation. Retention catheter. The temperature, pulse and respiratory rate, blood pressure and urine volume should be determined every two hours until the patient is conscious. Oxygen is administered for cyanosis.

Convulsions: At least two of the following drugs are used: Magnesium sulphate: 10 c.c. of a 25 per cent solution, intramuscularly and 5 c.c. after every convulsion until controlled. Luminal-sodium: subcutaneously, 0.3 gm. (5 gr.), every eight to twelve hours. Morphine sulphate: $\frac{1}{4}$ gr. every hour until convulsions cease or respirations become 12 per minute. Chloral hydrate: 2 gm. (30 gr.) in 100 c.c. of starch water are given by rectum every six to twelve hours.

Elimination: Soapsuds enema.

Hypertension: Sedation, especially barbiturates and chloral hydrate.

Renal and Cerebral Symptoms: The intravenous injection of from 500 to 1,000 c.c. of a 20 per cent solution of glucose, 2 or 3 times daily given within forty to sixty minutes. Sufficient glucose is injected to insure a urinary volume of at least

*Dieckmann, Wm. J.: AM. J. OBST. & GYNEC. 18: 757, 1929.

†Idem: AM. J. OBST. & GYNEC. 33: 165, 1937.

of toxemia, either hypertension, albuminuria, edema, or excessive gain in weight, was first noted at 33.5 weeks' gestation, and the eclampsia occurred at thirty-seven weeks. On examining the prenatal records of the 23 patients seen in our clinic, who subsequently had eclampsia, it was quite obvious that the internes did not interpret abnormal findings properly. These patients had adequate prenatal care, but it was not intelligent prenatal care.

The toxemia clinic was started in January, 1932, and we have been seeing most of the patients with toxemia. To date no patient who was seen in that clinic has developed eclampsia. Considerable discussion has arisen in the literature in regard to the value of prenatal care. None of us who have had experience in obstetrics doubts its value, but in view of the fact that its value is being questioned, a few comments are of value. At the East End Maternity Hospital in London, whose records go back to 1884 and which had a death rate in the nineties of 1.9 per 1,000 live births, the rate now is 0.68. Furthermore, in the last 10,000 consecutive deliveries only one case of eclampsia occurred and she had had no prenatal care for a period of three weeks.

According to the English classification, 33 patients had mild eclampsia and 19 the severe type. When the patient has eclampsia, one must decide early as to the course of treatment and cannot wait until there have been twelve fits, coma, temperature of 103°, etc. We classify as severe any case in which one of the following occurs:

Temperature of 39° C. (102° F.)

Coma

More than 10 convulsions

✓ Cardiovascular impairment (cyanosis, râles, low blood pressure)

Failure of "proper treatment" to

check convulsions

produce urinary output of 700 c.c. or more per twenty-four hours

prevent onset or deepening of coma

produce a blood dilution.

With this classification the figures were the same but 12 patients were transferred from one to the other class.

Termination of Pregnancy.—There were 10 cesarean sections and 6 vaginal hysterotomies and/or Dührssen's incisions. Thus our treatment of the condition is still rather active. At the old Chicago Lying-In 12 per cent of the cesarean sections were for eclampsia and toxemia. At the new Lying-In Daily gives 14.4 per cent for this group of patients.

Maternal Mortality.—Of the 3 patients who died one had had prenatal care. As is evident from the protocol, we did not attribute sufficient importance to the marked gain in weight. The other two patients had had no prenatal care, although one, who was in the hospital twenty-four hours before death, could probably have been saved if the pregnancy had been terminated shortly after admission.

Fetal Mortality.—There were 57 babies from the 52 pregnancies. Of these 12 were stillborn or died neonatally. Two mothers died undelivered. Thus 14, or 24.5 per cent, of the babies were lost. Of the total deaths 11, or 79 per cent, weighed less than 2,500 gm. One-half of all babies weighed less than 2,500 gm., and one-third less than 2,000 gm.

I have been collecting statistics on the geographic distribution of eclampsia and the other toxemias of pregnancy. The collective data (Table IV) for representative hospitals in the United States are of interest and suggest a number of questions. Why do the incidence and mortality in the hospitals vary? Is the eclampsia more severe in certain areas or do the doctors know less in these cities where the mortality is high?

To discuss briefly the question of prevention, it is true that one is impressed with the experience of Professor De Snoo with a salt-free diet, and with recent observations based on hormone assays. Yet as practical obstetricians it would appear to us that what is required, is first quick recognition of the very early forms of toxemia and immediate institution of treatment. Failing prompt recovery we must rid the uterus of its contents. There is also an urgent demand for a much more prompt and radical method of dealing with the chronic nephritis cases.

DR. OTTO SCHWARZ, St. Louis, Mo. (Read by the President).—In 1929 Schwarz and Dieckmann reporting from Washington University on the treatment of eclampsia stressed:

1. The importance of conservative management.
2. The relationship between blood concentration and unfavorable clinical signs and symptoms and vice versa the clinical improvement associated with blood hydration.
3. The advantage of grouping cases as mild or severe and establishing the fact that mild cases gave better end-results when treated conservatively, whereas severe cases gave better end-results if handled actively.

Since that report was made, or in the last seven years (1930 to 1936 inclusive) it has been the policy in this clinic to continue to emphasize conservative management of eclampsia, but to recognize also that certain fulminating cases (severe eclampsia) must be treated actively as they are in too critical a condition to survive a period of expectant waiting. Hence the following outline of treatment:

A. CONSERVATIVE MANAGEMENT

1. *Sedation*.—10 c.c. of 25 per cent $MgSO_4$ given intramuscularly (gluteus) immediately after the first convulsion. Repeat in 5 c.c. amounts after each succeeding convulsion until controlled. If patient is in coma or not having convulsions no intramuscular magnesium sulphate is given as it is considered simply a sedative.

2. *Elimination*.—Colonic irrigation using soapsuds or plain water until the return is clear. Gastric lavage using normal saline or a weak sodium bicarbonate solution until the return is clear. Before removing the stomach tube, introduce 60 c.c. of 50 per cent magnesium sulphate into the stomach, using retention catheter for accurate determination of urinary output.

3. *Dilution*.—1,000 c.c. of 20 per cent glucose intravenously, given in forty to sixty minutes, twice or three times daily, depending on response of patient. Higher concentrations of glucose (30 per cent or 50 per cent) may be necessary if diuresis is not established. This is particularly true if much edema is present. Usually 300 to 400 c.c. of the 30 per cent or 100 to 200 c.c. of the 50 per cent glucose is given at one injection. Careful check on heart and lungs *before* injection of any volume of intravenous glucose in excess of 300 c.c.

4. *Nutrition*.—Usually after twenty-four hours the patient will tolerate food and is given a diet consisting of fruit and fruit juices. Under no circumstances should any food or fluid be injected into the stomach if the patient is comatose.

5. Vaginal instillations of recently prepared 1 per cent neutral acriflavine in glycerin, 8 c.c. twice daily. This is in anticipation of any necessary manipulation from below.

To this point the treatment is entirely conservative with sedation, elimination and blood hydration being stressed. What the management will be beyond this point is entirely dependent on the response to the above measures. Usually twelve to twenty-four hours is sufficient time to show whether the patient can continue on a conservative regime with reasonable hope for a favorable outcome or whether active

30 c.c. per hour. Occasionally a 30 or 50 per cent solution in smaller amounts is necessary. Normal saline, Ringer's or bicarbonate solutions are *contraindicated*.

Pregnancy: If the patient is in labor, it may be hastened by rupture of the membranes or the use of a bag. If the patient is not in labor, we may, after a diuresis has been established, consider: (A) Induction of labor, as described above, or (B) cesarean section. This operation should only be performed if the case is of the severe type or if cephalopelvic disproportion exists. Local anesthesia should be used and the environment must be suitable.

Diet: Nothing is given by mouth until the patient is conscious. As soon as the stomach is emptying itself, 50 c.c. of a 10 per cent Karo syrup solution are injected through a nasal tube and increased 50 c.c. every hour up to the patient's tolerance (usually 200 c.c.) and continued until the patient is able to take water and fruit juices by mouth.

CONCLUSIONS

Prenatal care will not prevent nonconvulsive toxemia of pregnancy but it will, if the various abnormal symptoms and signs are intelligently interpreted, prevent the occurrence of eclampsia and severe preeclampsia.

The normal pregnant woman has a positive balance for water, sodium, and chloride. We do not know which is primary. In certain pregnant individuals the retention becomes abnormal and various symptoms and signs occur. A diet which contains so little sodium chloride that the twenty-four hour excretion in the urine is less than 3 gm. is efficacious in most patients in reducing the edema and preventing eclampsia.

A co-ordinated systematic study of the toxemias of pregnancy should be made under the auspices of the special societies or one of the research foundations.

DR. JOHN R. FRASER, MONTREAL, QUE.—In our clinic in Montreal from 1927 to the present time in about 20,000 cases there have been 104 eclamptic cases with 10 maternal and 35 fetal deaths. In that time the policy of the clinic has been to adopt a decidedly palliative plan of treatment. Of those 104 cases 69 were primiparous women with an average age of twenty-four and thirty-five multiparous with an average age of thirty-one. The average number of convulsions in the group was 3.5. The termination in 62 cases was by spontaneous delivery; in 42 by induction. Of the 42 induced cases, which obviously were severe, there was medical induction in 7, rupture of membranes in 20 and bag induction in 15. Where the labor was terminated it was done with the least possible disturbance, low forceps in 19, midforceps in 10, breech extraction in 4, and cesarean section in 3 cases.

Now if we contrast that series of cases with the period when a much more active, surgical treatment of eclampsia was in vogue, we see a very different picture. There were 129 cases when accouchement forcé was more in use. In 69 cases there was a mortality of 28 per cent, a fetal mortality of 62 per cent. Abdominal cesarean section was done in 13 cases, with 39 per cent maternal mortality and 15 per cent fetal mortality. Where palliative measures were adopted, there was a maternal death rate of only 2.3 per cent. It would appear from this small series of cases that the pendulum in our clinic has swung in the same direction that it has all over this continent and abroad. We are adopting gradually the general principle of the plan laid down by Stroganoff.

Unquestionably cesarean section is required in certain cases and under certain conditions, but in our view cesarean section has only a limited place in the treatment of eclampsia. We feel that eclampsia calls for a more palliative policy which would be governed by three things, namely moderate narcosis, moderate elimination, delivery at as early a date as is consistent with the condition of the individual patient.

opinion as to what is and what is not proper in the treatment of eclampsia.) This unfortunate state of affairs simply bears witness to the fact that no specific or entirely satisfactory treatment for eclampsia has yet been found. As regards prevention, the guest speaker's presentation pleads eloquently the cause of prenatal care. We at Washington University are forced to agree with Professor De Snoo that, in the light of our past experience, far more ultimate good in the prevention of death from eclampsia will result from efficient prophylaxis in the form of adequate prenatal care than could possibly be accomplished by the universal application of any one of the various current systems of treatment, once the eclamptic state has developed.

DR. H. J. STANDER, NEW YORK, N. Y.—I have nothing to say with regard to the etiology of eclampsia as I know nothing about it. I may say, however, that we have put no emphasis upon salt-free diet. We have come to a point of view in which we place no importance on the diet of eclamptic patients, but in spite of that our results are fairly similar to Dr. De Snoo's.

We have approximately the same number of cases that Dr. De Snoo referred to, so that our figures are comparable to those presented. The incidence of eclampsia in our clinic is 1 in 555 pregnancies, while that of preeclampsia is 1 in 119 pregnancies, giving an incidence for the whole disease entity "Eclampsia—Preeclampsia" of about one in every hundred deliveries in the Lying-In Hospital (Table I). This disease constitutes about 12 per cent of all toxemias, including the nephritides (Table II).

TABLE I. INCIDENCE OF ECLAMPSIA AND PREECLAMPSIA IN 17,201 PREGNANCIES

	NO. OF CASES	INCIDENCE
Eclampsia	31	0.18% or 1 in 555 pregnancies
Preeclampsia	145	0.84% or 1 in 119 pregnancies

TABLE II. INCIDENCE OF TOXEMIA (INCLUDING NEPHRITIS) IN 17,201 PREGNANCIES

	NO. OF CASES	INCIDENCE
All types	1448	8.4% or 1 in 11.9 pregnancies
Eclampsia and pre-eclampsia	176	1.02% or 1 in 98 pregnancies or 12.1% of all toxemias

TABLE III. VARIOUS TYPES OF ECLAMPSIA

TYPE	NO. OF CASES	PERCENTAGE
Antepartum	7	22.58
Intrapartum	13	41.94
Postpartum	10	32.26
Intercurrent	1	3.22
Total	31	100.00

TABLE IV. TYPE OF DELIVERY IN ECLAMPTIC AND PREECLAMPTIC PATIENTS

TYPE	ECLAMPSIA		PREECLAMPSIA	
	NO. OF CASES	PER CENT	NO. OF CASES	PER CENT
Spontaneous deliveries	11	36.67	74	51.03
Total operative deliveries:	19	63.33	71	48.97
Forceps, breech, etc.	10		44	
Cesarean section	2		16	
Induction	7		11	

intervention will be necessary. If there is no improvement or if the condition grows worse, then the patient must be considered a severe case and active obstetric interference is indicated.

B. ACTIVE MANAGEMENT

This means delivery of the patient.

(1) *Examination*.—To determine various factors pertinent to actual delivery: e.g., condition and parity of the mother, size of pelvis, size of baby, presence or absence of labor and the *condition of the cervix*.

2. *Delivery*.—(a) Patient in labor, general condition fair, cervix short and dilating. (1) Rupture of membranes, (2) insertion of bag, (3) oxytocic, and (4) forceps. (b) Patient not in labor, cervix firm, closed. Abdominal cesarean section *under local anesthesia*.

Postpartum Care.—Continue intravenous glucose to keep up satisfactory urinary output. Continue elimination from bowels.

If glucose even in 30 per cent to 50 per cent concentration fails to produce diuresis, phlebotomy 500 to 600 c.c. may be resorted to, but if done a donor should be ready, or the blood should be citrated as withdrawn from the patient.

In general no saline, Ringer's or bicarbonate solutions are to be given. Ninety cubic centimeters of 50 per cent magnesium sulphate, as a rectal tap six or eight hours if necessary, to decrease intracranial pressure if headache, convulsions or coma develop. If patient is very restless phenobarbital or sodium amytal by hypodermic is to be preferred to morphine.

If acidosis develops treat with sodium lactate solution: one part of a molecular solution of sodium lactate diluted with an equal or greater volume of 20 per cent glucose solution or distilled water (not Ringer's or saline for eclamptics) may be given intravenously in 300 to 600 c.c. amounts. If alkalosis develops treat with dilute hydrochloric acid, 1 to 5 c.c. dilute HCl being given in a small amount of milk or fruit juice every four hours. As an emergency treatment of alkalosis, calcium chloride may be given intravenously (25 mg. per kg. of bodyweight, or 0.5 c.c. of a 5 per cent solution per kg. of body weight). Do not give calcium chloride subcutaneously, on account of the possibility of slough. In either acidosis or alkalosis therapy the safest way to check the results of the therapy is to make repeated CO_2 and pH determinations on the blood.

In the seven-year period, 1930 to 1936 inclusive, 217 cases of preeclampsia were observed in the Washington University prenatal clinic. Of this group 26 or 11.9 per cent developed eclampsia. Of the 26 who developed eclampsia 2 or 7.6 per cent died. This mortality figure refers only to those patients receiving their prenatal and hospital care at Washington University.

In the same seven-year period four additional patients died of eclampsia on the Maternity Ward Service. Each of these latter 4 patients was admitted to the ward as an emergency without having had any prenatal care. Some idea of their critical condition when first seen may be appreciated from the fact that the average period of hospitalization for the four patients, from time of admission to time of death was 2.6 days. It is not necessary to comment further on these figures and the very important relationship between prenatal care and the incidence and clinical course of eclampsia that they imply.

The discussion of Professor De Snoo's paper was to include prevention and treatment of eclampsia. As regards treatment much is being advocated today that is not of universal approval. (One need probably look no further than the comments of those discussing this particular paper in order to find very important differences of

findings and the effect on these of the appropriate treatment, such as anti-acidosis therapy, diuresis by concentrated glucose and sedation.

It is quite possible that Dr. De Snoo is correct in his assumption that salt plays a part in the production of eclampsia. I believe that some eclamptic patients die from a marked acidosis that develops very rapidly, and if you follow the blood chemistry, you can prevent that acidosis. The patients die from three to five days later from marked liver destruction and the only way to treat that is by glucose therapy. A third of them die from complications other than the straight eclampsia, such as lung complications. I also believe that the effects on the kidney are secondary and not the direct effect of the eclampsia.

TABLE V. TREATMENT IN ECLAMPSIA AND PREECLAMPSIA

TYPE OF TREATMENT	ECLAMPSIA		PREECLAMPSIA	
	NO. OF CASES	PERCENTAGE	NO. OF CASES	PERCENTAGE
Conservative	16	53.3	73	50.4
Conservative treatment followed by induction of labor	12	40.0	56	38.6
Bag	3	10.0	8	5.5
Bougie	5	16.7	9	6.2
Medical induction	4	13.3	39	26.9
Conservative treatment followed by cesarean section	2	6.7	16	11.0
Total	30	100.0	145	100.0

TABLE VI. MATERNAL AND INFANTILE MORTALITY IN 177 CASES OF ECLAMPSIA AND PREECLAMPSIA

	ECLAMPSIA			PREECLAMPSIA		
	NO. OF CASES	NO. OF DEATHS	INCIDENCE OF MORTALITY	NO. OF CASES	NO. OF DEATHS	INCIDENCE OF MORTALITY
Maternal	32	0	0	145	0	0
Infantile		8	25%		16	11%

DR. PHILIP F. WILLIAMS, PHILADELPHIA, PA.—Dr. De Snoo offers an interesting theory on the etiology of eclampsia which refers to the consequences of the large amount of salt, 15 to 20 gm. a day, ingested by the pregnant women of the Netherlands, and which is probably accounted for by the large amount of salted butter common in the daily diet of that country. An informal survey of the salt content of the diet of some 200 clinic and private patients in Philadelphia showed only two or three women who estimated that they ate more than two teaspoonfuls of salt a day. Whether or not these women made correct estimations of the salt content of their diet, it is a fact that a recent assay of the food in complete house diet of one day at the hospital of the University of Pennsylvania showed the salt content to be only 6 gm.

It is an unmistakable fact that toxemias of pregnancy which reach a convulsive stage are diminishing. In Pennsylvania in 1930, 208 deaths were certified as due to eclampsia; in 1935, 104. In Philadelphia in 1931 there were 41 eclamptic deaths, in 1936, 21. In the United States as a whole over the same period, the mortality rate from eclampsia fell from 16.3 to 10 per 10,000 live births.

In the different sections of the United States, we find evidence of wide variation in the incidence of convulsive toxemia. In some Southern states the proportion of toxemia and eclampsia deaths to the total maternal mortality reached 45.

Intrapartum eclampsia appears to be twice as common as antepartum (Table III), but this is probably not so, as many cases of intrapartum eclampsia undoubtedly are actually antepartum eclamptics, in whom labor was brought on by the eclampsia. The three types, ante-, intra-, and postpartum eclampsia, are probably equally frequent, while the intercurrent form is very rare.

A study of Table IV shows that spontaneous delivery occurred in over one-third of the eclamptic, and over one-half of the preeclamptic patients. Cesarean section was performed in 16, or 11 per cent, of the 145 preeclamptic patients, and in only 6.7 per cent of those who developed convulsions.

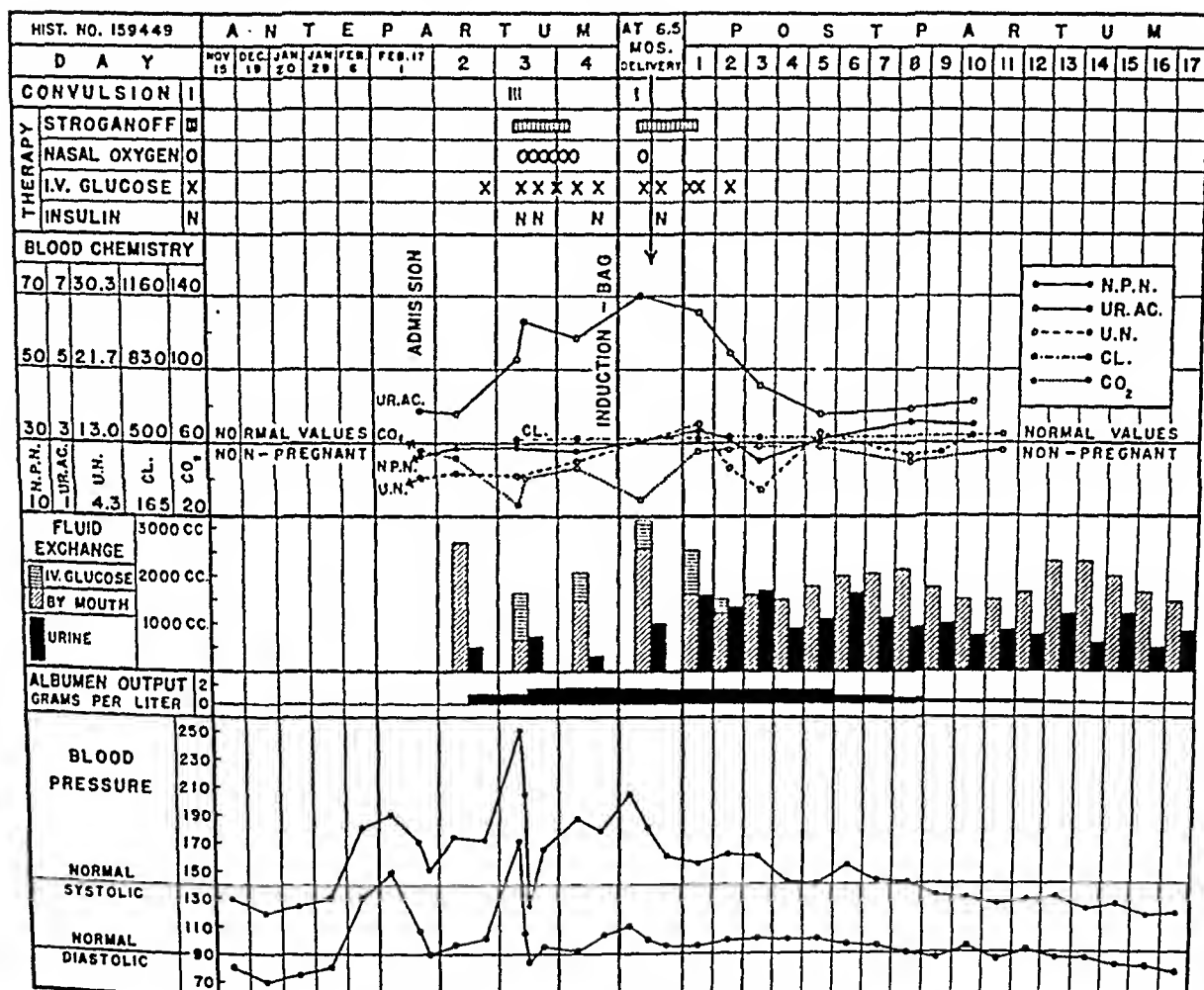


Chart 1.—Effects of therapy on various physical and chemical findings in a case of eclampsia.

Our treatment in eclampsia is conservative as shown in Table V. Over half of all our eclamptic as well as preeclamptic patients had conservative treatment only. In 40 per cent of the eclamptic and 38.6 per cent of the preeclamptic patients, the conservative treatment was supplemented with induction of labor (bag, bougie, or medical).

Our results from the time we opened the new Lying-In Hospital, Sept. 1, 1932, up to May 15, 1937, are presented in Table VI. During this period we treated 32 eclamptic and 145 preeclamptic patients, with no maternal mortality and with an infantile mortality of 25 per cent in eclampsia and 11 per cent in preeclampsia.

As we constantly utilize repeated blood chemical studies in the treatment of eclampsia, Chart 1 has been constructed to portray the variations in the chemical

the individual case will no doubt continue. The very best treatment of eclampsia lies in the prevention of the condition and this can be accomplished by efficient prenatal care.

DR. EDWIN F. DAILY, Director of Maternal and Child Health, Washington, D. C.—Newspapers, magazines, medical journals, and speakers throughout the entire country have for many years been focusing the attention of the people on the excessive maternal mortality in the United States. Most of this educational effort has been worth while and has resulted in a combined lay and professional realization of their joint responsibility in providing better care for pregnant women. In contrast there has been surprisingly little attention given to the constant lowering of our maternal mortality rate. Even if we only study the vital statistics for the years 1930 through 1935, years in which comparable, accurate, nation-wide figures are available, we find much to encourage us and considerable enlightenment regarding maternal mortality trends.

In this six-year interval the maternal mortality rate has been lowered 13.5 per cent; actually 2,292 fewer women died from all puerperal causes in 1935 than in 1930. Correcting this figure for lowering birth rates: if the 1930 maternal mortality rate had prevailed in 1935, there would have been 1,895 more maternal deaths in 1935.

Analyzing this steady and significant decrease in maternal mortality from 1930 through 1935 gives us some striking figures. The mortality rate for all puerperal sepsis decreased only 1.6 per cent. The mortality rate for puerperal hemorrhage decreased only 7.2 per cent. The mortality rate for puerperal albuminuria and eclampsia decreased 36.8 per cent. The marked decrease in deaths from eclampsia actually accounts for 54 per cent of the decrease in the number of puerperal deaths in 1935 compared to 1930.

In the urban areas of the United States 15.4 per cent of all puerperal deaths are assigned to albuminuria and eclampsia, while in rural areas 23.6 per cent are assigned to this cause.

Studying the percentage of all puerperal deaths which were assigned to puerperal albuminuria and eclampsia in the various states, we find that this percentage is highest in eight southern States. In fact, 55 per cent of all toxemia deaths in the United States occurred in the seventeen southern States in 1935, whereas only 37 per cent of the live births occurred in the same area. One of the most important factors in this distribution of deaths from albuminuria and eclampsia is indicated by the figures which show that, although 24 per cent of the deaths from toxemia in the United States are negro, yet only 12 per cent of the live births in the United States are negro.

DR. GEORGE W. KOSMAK, NEW YORK, N. Y.—Two points in Dr. De Snoo's paper interested me very much, namely his reference to the importance of prenatal care and his subsequent statement that owing to State-wide attention to this subject they have prevailed upon women to come for examination at the seventh month. Most of us in this country would have an eclamptic convulsion ourselves if we did not succeed in getting prospective mothers to apply for prenatal care before the seventh month.

I believe, however, that we have somewhat exaggerated the value of prenatal care in obstetric practice and that we must give as great attention to intrapartum care in the future as to prenatal care. There is no question that so far as eclampsia is concerned, the better hygiene has resulted most favorably, but the good results do not seem to be apparent in any reduction of the puerperal deaths, particularly in those due to sepsis and hemorrhage.

per cent, while in a midwestern city eclampsia is so rare that it has been found necessary to solicit such cases for educational purposes.

Where prenatal care reaches its highest degree of efficiency eclampsia falls to low statistical levels. The searching for and hospitalization of minor degrees of toxemia early in pregnancy will maintain admissions for toxemia of pregnancy at a fair level, but we will find marked diminution in the number of patients admitted in, or developing, a convulsive state. The hospital clinics in the city of Philadelphia from 1932 to 1934 carried 34,310 prenatal cases with 534 or 1.5 per cent developing some form of toxemia; 85 or 0.25 per cent developed eclampsia and of these 10 women died. It is evident therefore that the observation and treatment given these patients was responsible for the minimal death rate from eclampsia.

At the hospital of the University of Pennsylvania over a period of fifteen months in a total of 1,700 deliveries, there were 35 diagnosed as hypertensive pregnancy toxemia, 59 diagnosed as hypertensive vasculorenal diseases including nephritis. Thus we have an incidence of 5 per cent for admissions of various types of toxemia in late pregnancy. Four in the first group were regarded as preeclamptic and one emergency admission as postpartum eclampsia. This latter case represents the one mortality in the pregnancy toxemias series, and there was also one mortality in the hypertensive vasculorenal disease group. The present feeling of our clinic is that the division of "hypertensive pregnancy toxemia" and "vasculorenal hypertension" is artificial, and that future studies may show "toxemia" to be merely a phase in the development or course of underlying vascular disease.

Such cases are admitted from the prenatal clinic for study on the finding of albuminuria, hypertension, or excessive weight gain. The arbitrary limits we use are posted in the clinic and are taught to the students. Through the efforts of the Committee on Maternal Welfare of the Philadelphia County Medical Society similar standards for admission and study for potentially toxic patients have been widely adopted in the clinics of Philadelphia. At the Hospital of the University of Pennsylvania the routine studies on admissions include such clinical observations and laboratory examinations as are felt may throw light on the diagnosis and prognosis of the particular case of toxemia. The initial basic treatment of our cases consists in bed rest, house diet, and individually indicated measured intake of fluid, sedation and required intestinal elimination by salines.

The interruption of pregnancy in the various grades of toxemia is particularly individualized in the University of Pennsylvania Hospital. Each case is considered on its own merits. Briefly, increasing hypertension, systolic or diastolic, increasing albuminuria, and continuing signs of renal dysfunction are our main guides. Toxemic pregnancies are interrupted at the thirty-sixth week, or before, only in the presence of blood pressure above 160 systolic or 110 diastolic after continued bed rest of ten days or more, and in spite of the absence of other unfavorable findings.

Our treatment of the eclamptic attack would be conservative except for obstetric indications, and we would terminate pregnancy in such conditions only after recovery from the acute eclamptic attack. If recovery did not follow medical treatment of the acute eclamptic attack, we feel that obstetric treatment would not save the patient.

This conservative therapy is closely in line with the practice of the members of the Philadelphia Obstetrical Society which was reported some years ago by a survey of the treatment of eclampsia by the members of the Society. This showed a widespread tendency to conservatism with the resulting mortality of 5.4 per cent of all late toxemias and 21 per cent of all convulsive or comatose cases.

Until the etiologic factors of eclampsia have been discovered there can be no causal therapy for this symptom complex and a therapeutic negativism based on

THE STILLBIRTH PROBLEM*

PHILIP F. WILLIAMS, M.D., PHILADELPHIA, PA.

DURING the past decade there has been a marked increase in the attention paid to maternal welfare and maternal mortality in the United States. More particularly the attention of the medical profession has been focused on their own communities as individual areas for study, so that at the present time there have been given to us reports of the circumstances regarding maternal deaths from widely separated portions of the United States. These studies have enabled us to draw conclusions regarding various problems of maternity care, and to note the special factors which seem to influence the varying proportion of deaths from one cause or another in different sections of the country.

As an analysis of maternal deaths is carried on in a community, certain associated or closely related problems or phases of maternity care begin to stand out prominently, and suggest themselves as separate topics for study and discussion. One of these problems is the amount and quality of prenatal care furnished by the facilities of the community. It is not difficult to assess the maternity care given to ward patients whose hospital records are available for study, on the other hand it is quite a different matter to attempt to evaluate the care given to pregnant women by private practitioners. A second problem of note is the extent of maternal morbidity following delivery, and the standards by which such maternity morbidity is established. A third might well concern itself with the loss of infants within a short time after birth, due for the most part to causes immediately connected with pregnancy and parturition. A fourth, but not necessarily a final problem, is that of the fetal mortality we term stillbirths, which I wish to discuss this evening.

When the statistical report of the first three years' study of maternal mortality in Philadelphia was prepared, the impressive, but not necessarily surprising, fact appeared that approximately eight times as many maternal mortalities occurred in connection with women who gave birth to dead fetuses as when a live baby was born. Some consideration of the circumstances surrounding stillbirths in Philadelphia has seemed necessary and such consideration would be appropriately timed, in view of the fact that the Children's Bureau of the Department of Labor is engaged in a nation wide study of this subject. It is recognized that in the last twenty years there has been a marked

*Read at a meeting of the Brooklyn Gynecological Society, March 5, 1937.

DR. JAMES R. McCORD, ATLANTA, GEORGIA.—After seeing all of those blue spots on the chart presented by Dr. Daily, showing the large number of deaths from eclampsia in the South, particularly among the colored women, I must speak. The chart was interesting to me because Stander and Schwarz have always said that the disease is milder in the negro than in the white woman. This is not our experience.

In our present series we have had 164 consecutive cases of eclampsia in colored women with a total uncorrected mortality of 6.7 per cent. All these women had convulsions except one and the diagnosis of eclampsia in that woman was made at autopsy. Two cesarean sections were done in the series, both in 1928. A cesarean section has not been done in our clinic for eclampsia or preeclampsia since that time. Forceps deliveries were done 18 times. The remainder of the women delivered spontaneously.

We treat with one dose of morphine, magnesium sulphate, the dextrose solution. As soon as the convulsions are controlled labor is always induced. We do not see any use in tempting Providence further. We thoroughly believe in the conservative treatment of eclampsia.

PROFESSOR DE SNOO (closing).—That so many of my colleagues have participated in this discussion shows that eclampsia has the full attention of our profession here in America. I have seen this also in your literature. Your mortality figures in 1928 or 1929 showed that 5,000 women died from eclampsia. Last year the rate had diminished to less than 50 per cent. That is the best proof that the clinical care of your patients is very good.

Dr. Kosmak said that it is too late to have these women come in at the seventh month. He is entirely right and we endeavor to see those patients earlier wherever possible, particularly those whom we know have hypertension. But with the great mass of patients I think it is best to ask them to come at the seventh month, and then four or five times later because the last months are the most important. It is during the last months when eclampsia occurs and that is the reason we really begin with observation in the seventh month.

Feenders, H.: Hydatid Mole in a Fifty-Five-Year-Old Woman, *Zentralbl. f. Gynäk.* 60: 2308, 1936.

Feenders states that many authors believe that hydatid moles occur more frequently in pregnancies of older women, although in reviewing the literature it may be seen that they occur relatively infrequently in women past fifty years of age.

The author reports the case of a fifty-five-year-old woman whose past history is essentially negative. She had six full term pregnancies, the last of which was a placenta previa, and four abortions. During the fifth month of the present pregnancy, the patient came to the clinic for vaginal bleeding. The diagnosis of climacteric bleeding was made. After no improvement with administration of ergot, a curettage was performed.

Peculiar grayish white pieces of tissue were obtained which on microscopic examination proved to be parts of placental tissue undergoing hydropic degeneration. The diagnosis of hydatid mole was made and the patient kept under close observation. Urine afterwards gave a strongly positive Aschheim-Zondek reaction. Five weeks later the uterus and the adnexa were removed, but the removed specimen showed no evidence of a chorionepithelioma.

The author feels that in similar cases the removal of uterus and adnexa is definitely indicated.

RICHARD E. SOMMA.

problem in the United States was the most neglected one in the whole field of infant mortality, and that the stillbirth problem was one of greater magnitude than that of neonatal deaths. She stated that the stillbirth rate for the seven years for which such statistics had been kept formed practically a straight line. Since that time the birth registrations area of the United States has expanded to 100 per cent representation of the population. In 1922, with only 72 per cent of the population represented in this area, the stillbirth rate was 39 per thousand livebirths; in 1934, the last year for which figures are available, and at which time a 100 per cent population area was covered, the stillbirth rate was 36. The total number in 1922 was 70,010; in 1934, 78,503. The rates for the United States, over this period of years, and for the two states, New York and Pennsylvania are shown graphically in Fig. 1.

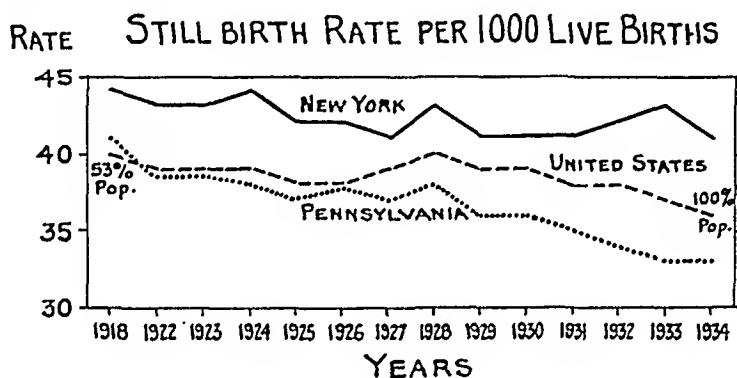


Fig. 1.

Since we have looked at the United States as a whole in regard to the rates and totals of stillbirths for a period of years it is well to examine into the rates shown by the various states for recent years, together with the definitions used for classification of stillbirths in the different component units of the United States. The basis of the study of the Children's Bureau was every fetus of twenty weeks' or more gestation born without signs of life, in the cooperating hospitals. The period of gestation and the definition of the stillbirth given for the schedule comes from rulings of statistical practice adopted by the American Public Health Association, namely, that a stillborn child is one which shows no evidence of life after complete birth (no breathing, no action of the heart, no voluntary action of any muscle). Birth is considered complete when the child is altogether, head, trunk, and limbs outside the body of the mother, even if the cord is uncut and the placenta still attached. The report of the Committee on Stillbirths of the American Public Health Association states that unless gestation has advanced to the fifth month, that is, 120 days, the product of the pregnancy need not be reported as a stillbirth.

decrease in the death rate of infants under one year, and a smaller decrease in the death rate for the first two weeks of life. But there has been practically no change in the rate for stillbirths since vital statistics on this subject have been collected.

With this fact in mind the Children's Bureau has begun a study of stillbirths in order to obtain statistical information regarding fetal and maternal conditions associated with fetal mortality in hospitals, to try to make possible the development of a classification of causes of stillbirth (fetal and maternal), and to further the development of a special certificate for registration of stillbirths which will serve as a base for comparable statistics for the various states. This study has been stimulated by the recommendations of a Sub-Committee on Stillbirths of the American Public Health Association which for some years has endeavored to have a uniform definition adopted in order to provide for comparability of records and to promote completeness in registration and uniformity in the use of terms. To provide a widespread sampling of the statistics hospitals in different areas of the United States have been asked to cooperate in returning completed schedules for their stillbirths in which the twelve questions asked should develop many pertinent facts on stillbirths.

The standard certificate of stillbirth proposed by the above-mentioned committee carries on its face the usual questions of the standard birth certificate of the United States Birth Registration area together with the additional questions which came in use on the first of January, 1937, and which appear to deal more with the data of social security than medicine. On the figure showing the stillbirth study schedule the questions are checked which are also found on the face of the proposed new certificate of stillbirth. There is one exception in that the schedule specifies under operations, "breech extractions," while the certificate specifies, "breech delivery."

On the reverse of the proposed standard certificate of stillbirth are found two groups of causes for stillbirth: (A) those determined in the fetus such as infection, asphyxia, malformation, birth injuries and other causes, or unknown, all of which are subdivided; and (B) causes and conditions in the mother associated with the fetal death which are divided in sixteen groups in accord with the terminology of the International List of the Causes of Death. The eleventh group specifies the diseases of pregnancy and childbirth which are most largely responsible for or associated with stillbirths. It is recognized by the Sub-Committee on Stillbirths of the American Public Health Association that this list of causes of deaths from the standpoint of both the fetus and the mother is tentative, and will probably be subject to revision after the certificate has been studied experimentally in some selected lying-in hospitals and cities. The adoption of such a certificate should naturally be followed by a study by vital statisticians of the proportionate causes of stillbirth with a resulting influence, one feels, toward a reduction in the present number of stillbirths.

In 1931 Dr. Sterling, speaking for the United States Public Health Service, at a Child Congress in Peru, concluded that the stillbirth

If we find varying definitions legal by states we find almost as wide variation in terminology and usage in medical studies of stillbirths and in hospital reports. A lack of uniformity or adherence to a common standard makes it difficult, if not impossible, to compare the results from one type of practice in a certain problem of obstetrics, as breech delivery, with the results achieved from another when the reports emanate from different clinics or cities. In most of the recent contributions on fetal mortality in medical literature one finds both a gross fetal mortality and a corrected fetal mortality set forth. Such corrections may be without apparent regard for the state definition of the stillbirth, and we find that individual authors correct their fetal mortality rate by subtracting variously all cases of macerated fetuses or congenital deformities or all prematures, which latter are listed arbitrarily according to length, weight, or period of gestation. Again

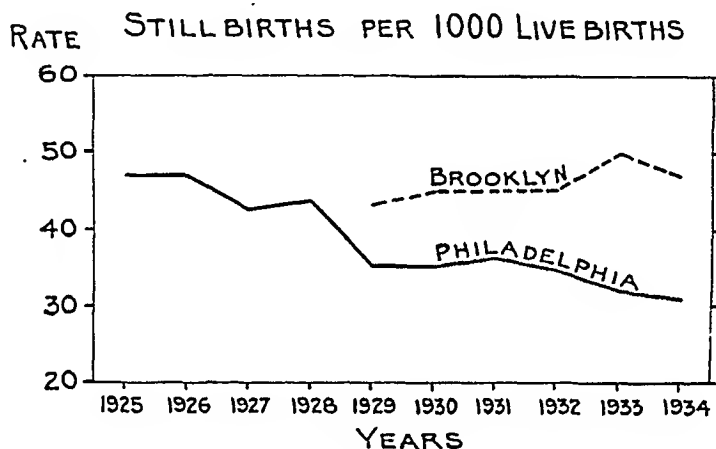


Fig. 3.

all twin pregnancies or emergency admissions have been eliminated or there have been subtracted all fetuses regarded as nonviable, and here again the definition of viability differs greatly. Some of these corrections do not appear justifiable.

The Pennsylvania definition of a stillbirth is a fetus which is past the fourth month, which does not show any sign of life without defining, however, whether the heart beat is a sign of life. In the state of New York any dead fetus advanced to the fifth month is regarded as a stillbirth, but the exception is made that this ruling is exclusive of New York City where any product of conception is requested to be registered. The stillbirth rates for Philadelphia and Brooklyn for the past few years as reported under the present definitions are shown in Fig. 3. It is probable, and very likely, that the higher stillbirth rate for Brooklyn is due to the disadvantage of this city in having to include any product of conception in its registrations of stillbirths. It is worthy of comment, however, aside from the definition that the rates of the two cities do not seem to have diminished appreciably in

In the accompanying outline map (Fig. 2) of the states, there are shown the varying periods of gestation at which they consider the product of conception stillborn as indicated by the upper figure, while the lower figure shows the stillbirth rate in each state for 1934, the last year for which figures are available. It will be seen that the majority of states accept the definition of the American Public Health Association that the pregnancy should have advanced to the fifth month, although there are other definitions which range from no definite rulings as to age, to any product of conception, to sixteen weeks, or twenty weeks, advanced to the fourth month, past four months, about the fifth month, about the sixth month and in, or past, or over the seventh month. Consequently, it is apparent how indefinite and conflicting studies of stillbirths from individual states would

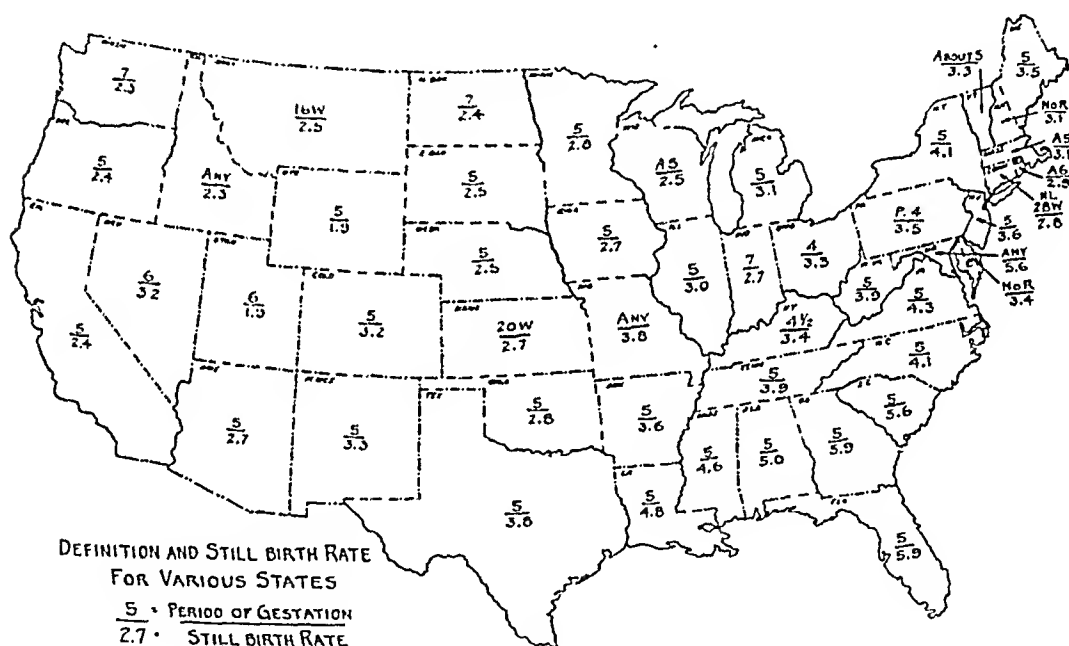


Fig. 2.

become and how useless comparisons might be from the standpoint of obstetric practice. There is a wide variance in the definition of stillbirths from different states. Some consider the birth of a fetus whose heart is beating but which does not breathe, a stillbirth, while in other states the fact that the heart of the fetus beats after birth makes it a livebirth, and its death with the cessation of heart action a neonatal death.

The two most prominent authors from the investigative aspect of the problem of stillbirths in England may be quoted. Holland states, "a fetus becomes an infant, child, or baby as soon as it has breathed. The fetus dies when its heart ceases to beat." While Ballantyne, who may be considered the original investigator in antenatal pathology states that "the term stillbirth should be applied if a child is 'still' but with discoverable signs of life, such as beating heart, and the term dead births should be applied if life is actually extinct."

in the past two years of our survey was reduced 41 per cent, in the first year and 28 per cent in the second year.

It may be of interest that in 64 women in the first survey in Philadelphia who died as primiparas after stillbirth that there was an operative incidence of 84 per cent, that the three largest causes of death among those primiparas were sepsis in 18, toxemia in 20, and accidents of labor in 11. It is significant, too, that of 80 multiparous women who died after stillbirth one out of four had had previous stillbirths. Of the deaths in the first Philadelphia survey, in 98 cesarean section deaths there were 25 stillbirths, in 112 forceps deaths there were 42 stillbirths, in 65 version deaths there were 34 stillbirths and in 36 multiple operation deaths there were 19 stillbirths.

To study a series of stillbirths in an institution with which I am connected I have applied the schedule of the Children's Bureau to the

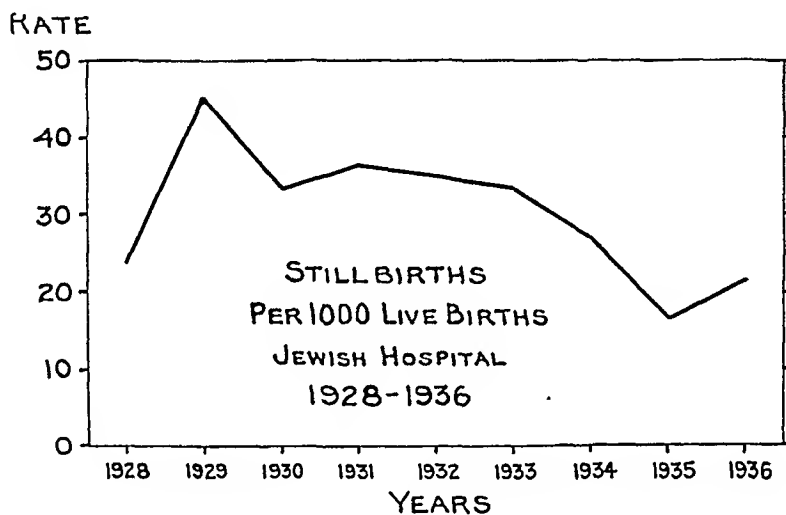


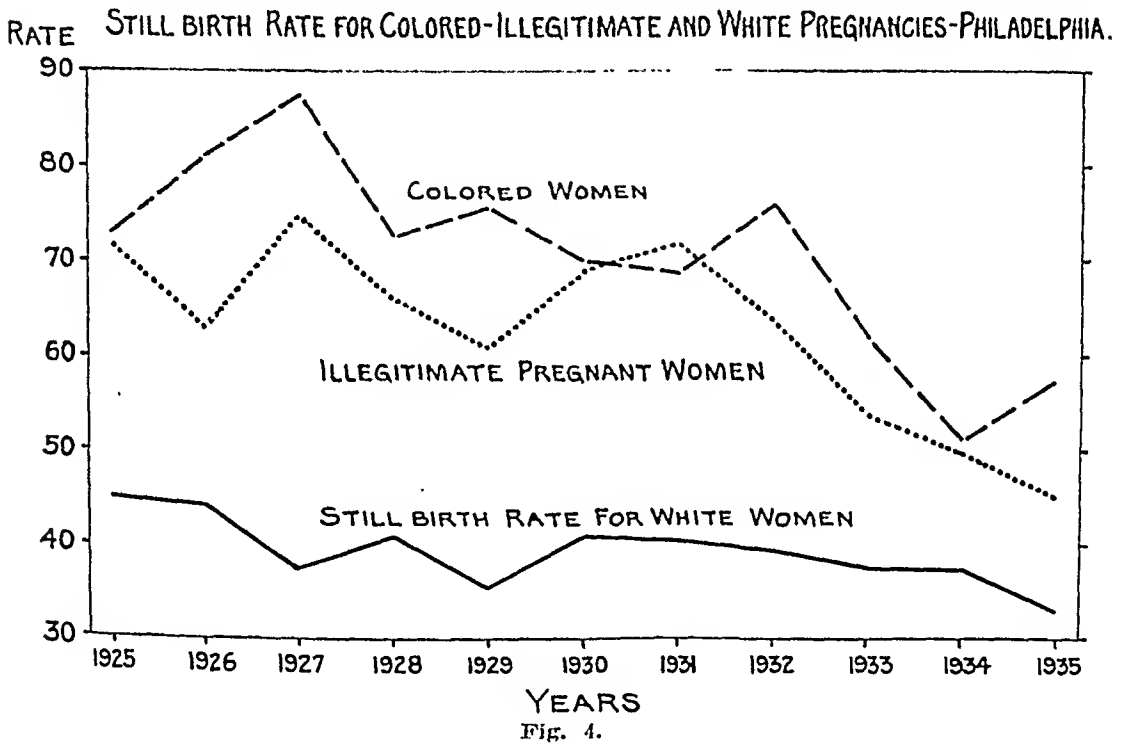
Fig. 5.

stillbirths which have occurred in the maternity division of the Jewish Hospital of Philadelphia, since it was opened, June 1, 1928 to Jan. 1, 1937. This has been conducted as an open service for ethical practitioners of the neighborhood, who cared to use the facilities of the maternity. It is only in the last three years that there has been any definite degree of supervision over, or regulation of the courtesy staff in their obstetric practice. At the present time the basic requirements of the American College of Surgeons for maternity divisions of hospitals are fairly effective in this institution although even yet there is some question at times of the qualifications or practices in the courtesy staff. I believe that the reduction of the stillbirth rate beginning 1934 is a result of a more stringent regulation of maternity practice adopted in the hospital. The stillbirth rate for the hospital, 28.8 in 7,895 deliveries, is shown in Fig. 5.

From this rather small series of 228 stillbirths probably basic deductions should not be made, and for the sake of comparison I will quote

recent years in spite of the attention which has been given to enlarge the amount and quality of antenatal care, and the increase of hospitalization for delivery in both cities.

A marked disparity in the stillbirth for the white and colored population in Philadelphia is shown in Fig. 4. The stillbirth in illegitimate pregnancies is inordinately high. Philadelphia is considered to have the largest colored population proportionately of any city north of the Mason and Dixon line. Since the maternal death rate among colored women in Philadelphia during our reported study was 7.2 as contrasted with an average of 6.2 in the white women it would seem that the excessive disparity between the stillbirth rates of the two races needed some study. The maternal mortality rate and the stillbirth in illegitimate



pregnancies were more nearly on a par, the maternal mortality rate being twenty, or over three times that of the legitimately pregnant women, while the illegitimate stillbirth rate was proportionately as high.

In contrast to the slight decrease in the stillbirth rate, it is a fact that the deaths from birth injuries in Philadelphia have shown a definite increase in the past few years. Whether or not this is due to a more careful and accurate reporting I do not know, but at any rate as hospitalization for delivery in Philadelphia has increased, the death rate of infants from birth injuries stepped up proportionately. During the period of our survey we found that the maternal mortality rate was almost eight times as great in women who gave birth to stillborn children as those delivered of live babies. As evidence of the effect of the continuing survey on maternal mortality in Philadelphia, we note that the death rate in women who gave birth to stillborn children

A postmature infant is a baby:

1. More than 4,500 gm. in weight.
2. More than 43 weeks.
3. More than 54 cm. long.

Any infant that fulfills any two of the three criteria in any group shall be classified in that group.

LABOR

The time of fetal death with respect to labor was recorded in 93 per cent of the 228 records. In 78, or 34 per cent, death occurred before labor; in 136, or 59 per cent, death occurred during labor; while in 14 cases, or 7 per cent, the record was incomplete on this detail. In the Bureau study 56 per cent occurred prior to labor, during labor in 37 per cent, with 7 per cent, no labor or not recorded.

OPERATIONS

In this series of 228 stillbirths, 127 fetuses, 56 per cent, were delivered spontaneously and 101, 44 per cent, were delivered by operative procedure. Forceps, 49 per cent, was the most frequent type of operation of the operative procedures, followed by version, 20 per cent; breech extraction, 16 per cent; cesarean section, 10 per cent; craniotomy, 5 per cent. In the Bureau study 62 per cent were delivered spontaneously, and 38 per cent by operative procedure; divided into forceps, 35 per cent; breech, 25 per cent; version and extraction, 14 per cent; and cesarean section, 12 per cent; with the remaining percentage not stated.

The figures of one class almost reverse the findings of the schedule study by the Bureau; there it was noted that in 73 per cent of the stillbirths in which the fetus was delivered by operative procedure the fetal death had occurred prior to the operation. In our series fetal death occurred in 37 per cent before operation was performed. A conservative obstetrician can only speculate as to the indications leading to the high figure, 73 per cent, arrived at in the Bureau study.

In this series the fetal death occurred during 64 per cent of the operative procedure. Such cases demand an intensive introspection by a hospital staff. They should not be regarded as an unavoidable group, but rather as a remediable group. Either the time of operation, or its selection or performance must have been largely responsible for many of these fetal deaths. It seems difficult to believe that one-fourth of the high forceps operations and 41 per cent of the versions should have been associated with fetal death.

There were 25 surgical inductions of labor, 11 per cent of the series, most of these were done by the method of Slemmons, with rupture of the membranes; a few labors were induced by bags or bougies. The majority of the indications were clear-cut, toxemia, nephritis, or medical conditions. The deaths were almost equally divided between the before labor group, and the during labor group. There were, four cases in which inductions were done at term, for which the record gives no clear indication where the fetus died during labor. It is to be surmised that these inductions represent the convenient group and the deaths serve to prove, even though a small percentage of the number of cases induced, that the induction for convenience is not without its dangers. In one of these cases 30 gr. of quinine were given during a period of four hours. The fetal death, the disappearance of the heart sounds, was noted one hour after the quinine was administered and before labor was established. This is the only instance in the many cases in which quinine was administered in medical or surgical induction where it was felt the drug might have played a part in the fetal death.

occasionally, through the courtesy of Dr. Elizabeth Tandy, the findings regarding similar items from a preliminary analysis on the first 1,000 stillbirth schedules received at the Children's Bureau.

With respect to race, our series is almost uniformly white, for the hospital is situated in a residential section free of slum areas or black belts. The Bureau reports 81 per cent white and 19 per cent colored in 1,000 schedules. If my study was from the Philadelphia General Hospital service the figures would be almost the reverse of the Bureau figures for race. The age groups in our series, 33 per cent under twenty-five years, and 50 per cent from twenty-five to thirty-four years, were almost exactly those in the Bureau study.

There were 111 primiparas in our series, 48 per cent, as compared with 43 per cent in the first 1,000 schedules studied by the Bureau and 36 per cent of the total stillbirths registered in the United States in 1933; and 117 multiparas, 52 per cent. This grouping in our almost entirely white survey show our stillbirths were in young women, twenty-one to thirty and that this series is almost equally divided between primiparas and multiparas.

Since our tabulations were carried on the same uniform base as the Bureau study we may compare our figures as to the period of gestation (Table I).

TABLE I

	NUMBER	JEWISH HOSPITAL PER CENT	CHILDREN'S BUREAU PER CENT
20—27 weeks' gestation	57	25	18
28—35 weeks' gestation	53	23	31
35—40 weeks' gestation	113	49	46
Postmature	5	2	5

In defining a postmature fetus we have accepted the definition recently suggested by Adair to the Chicago Board of Health. His classification was requested for a study of the causes of infant mortality, and after a failure to find any sufficiently satisfactory or uniform criteria for the purpose.

A previable premature is:

1. From 400 to 1,000 gm. in weight.
2. From 22 to 28 weeks.
3. From 28 to 35 cm. long.

A viable premature is:

1. From 1,000 to 2,499 gm. in weight.
2. From 28 to 37 weeks.
3. From 35 to 47 cm. long.

A full-term infant is a baby:

1. From 2,500 to 4,499 gm. in weight.
2. From 38th to end of 43rd week.
3. From 47 to 54 cm. long.

In 6 no cause was elicited or recorded for the previous stillbirth or stillbirths. In 4 nephritis had been present. In one there had been 8 stillbirths. In one a cesarean section had resulted in a dead baby after a long first labor. In this second pregnancy the uterine scar ruptured to produce a second stillbirth. Two were syphilitic. In one each there was previous dystocia, diabetes, repeated miscarriages, pelvic infection, pelvic injury. Undoubtedly, enough attention had not been paid to the previous history to prevent a stillbirth in the present pregnancy.

In the histories of 80 multiparous women who died after giving birth to a dead fetus, shown in random files pulled from the Philadelphia maternal mortality study, there were no significant facts in slightly over one-fourth of the cases, but the remainder had histories of previous dystocia, operative deliveries, toxemias, nephritis, repeated stillbirths or miscarriages, large babies, or even extreme multiparity, 6 to 16 pregnancies, items single or combined to form a total of 75. Certainly this was a sufficiently suggestive background to have provided enough warning that both baby and mother should not have been lost.

COMPLICATIONS OF PREGNANCY

So far as the complications of pregnancy as a productive factor in stillbirths are concerned, it is not possible to obtain them fully in this series. Many of the patients were in charge of private physicians, and their prenatal records, although added to the chart by compulsion of an order of the Pennsylvania State Board of Medical Education and Licensure, are frequently incomplete.

In the charts, 80 in number, where such notations were made, it was found that 24 women had a history of vaginal bleeding, these were almost all in the group from the twentieth to twenty-seventh week, there were 4 instances of abruptio placentae and 5 of placenta previa. In the toxemia group there were 12 cases of toxemia, of which 4 patients had convulsions, 4 had hypertension only, and 7 had nephritis. There were 6 instances of diabetes, 1 of cardiac disease, and 1 of hyperthyroidism. There were single instances of fibroids, pyelitis, tuberculosis of the spine, influenza, appendicitis, and fracture of the dorsal spine. In many, probably the majority of these complications the abnormal or associated morbid condition played a definite contributing influence toward a stillborn fetus.

In the Philadelphia report on maternal mortality of 1931 to 33 it was noted that the direct puerperal causes of death were associated with 349 contributing obstetric or medical conditions, equal to 54.6 per cent of the puerperal deaths. Just as complications of pregnancy influence the outcome for the mother so they also act for the fetus. In examining the records of the Cook County Hospital in Chicago, Allen and Bauer found the gross fetal mortality rate among normal patients to be 1.8 per cent while among patients with a concurrent medical condition it rose to 3.7 per cent. In other words a child born to a woman suffering with a medical disease is twice as likely to be stillborn as a child born to a normal woman.

Information regarding the use of drugs and anesthetics during labor and delivery is requested in the Children's Bureau schedule. In reviewing the cases in this series from this standpoint, I have analyzed critically the cases in which definite fetal or maternal states or operative manipulations did not apparently cause the fetal death. It would not be a quickly accomplished task to affirm that the Gwathmey method here, or the use of barbiturates there, or inhalation anesthesia, gas or ether, has caused any individual fetal death. Many times the same technic of sedation or anesthetization has been used safely; therefore in the deaths with obvious causative factors missing, one hesitates without more personal knowledge of

LABOR OVER TWENTY-FOUR HOURS

The influence of prolonged labor on stillbirth is well exhibited by the histories of the 47 cases where the labor exceeded twenty-four hours. Of these cases, half of which had operative delivery, 16 died of intracranial hemorrhage, 5 of asphyxia, and three of birth trauma. At the present time the hospital has a regulation calling for obligatory consultation at the end of twenty-four hours' labor. I am of the impression that this arbitrary time limit is too long, and that it should be eighteen hours or less, and that an arbitrary limit as to time will occasionally defeat the original purpose in allaying anxiety about the possible condition of a patient until serious cerebral trauma in the fetus may have occurred. Possibly an obligatory consultation for any marked alteration in the fetal heart rate would add in further protecting the fetus.

No note was made in this series as to the incidence of contracted pelvis. However, Peekham states that in a study of border line pelvis with vaginal delivery the fetal mortality rate in labors of twenty-four hours or less was 7.19, a figure less than $1\frac{1}{2}$ per cent above the rate pertaining to the general clinic mortality. In labors of thirty hours or more the fetal mortality rate rose to the appalling figure of 19.23 per cent gross.

MULTIPLE PREGNANCY

In the 7,895 deliveries from which this series of 228 stillbirths are drawn, there were 47 twin deliveries, an incidence of 0.6 per cent. Of these 94 fetuses four, one pair, and two singles, both second in order of birth, were stillborn. The pair of twins were syphilitic, the singles in twins died of asphyxia during a breech extraction, and from intracranial hemorrhage during a midforceps delivery. For these two operative deliveries no indication is recorded, other than to deliver a second fetus. In each instance the first fetus had been born spontaneously. In the United States Birth Registration area for 1933, in 4.5 per cent of twins both fetuses were born dead and in 4.2 per cent, one fetus of twins was born dead.

SYPHILIS

While the Bureau study showed 95 per cent reporting as to whether a Wassermann reaction had been made, in our series only slightly over half, 106 cases, showed this serologic test to have been applied. Of these only three were positive. There had been no antenatal treatment in these cases, and the fetuses at autopsy, including one set of twins, gave unmistakable evidence of syphilis. In the remaining cases there is no record of the test or it was applied after the delivery of a dead baby.

In the South Carolina study on maternal welfare it was shown, in contrast to these figures, that 22 per cent of the clinic patients had positive serologic tests, while McCord, in a series of fetal autopsies in Atlanta, reported 57 per cent with positive findings of syphilitic infection. Such figures show the broader implications of a nationwide survey or on a smaller scale, of a city wide survey, where the regional discrepancies in types of patients may be merged into a fairly approximate picture.

Parran feels that with universal serologic tests on all pregnant women, and with appropriate antenatal treatment, new cases of congenital syphilis could be eradicated in a decade.

PREVIOUS STILLBIRTHS

It is not without interest to inquire into the previous histories of the women in this series for whom at least one previous stillbirth was recorded on the birth certificates. They number 18, or approximately 8 per cent of the series.

in the mother associated with the fetal death. The causes determined in the fetus are divided into six groups:

A.		
1. Infections		5
Syphilis	4	
Septic infection	1	
2. Asphyxia		37
Separation of placenta	13	
Abnormalities of cord	17	
Other causes of asphyxia	7	
3. Congenital Malformations		14
Hydrocephalus	2	
Anencephalus	9	
Spina Bifida	1	
Other malformations	2	
4. Birth Injury		76
Malpresentations	7	
Difficult labor	62	
Other causes of physical injury to fetus	7	
5. Other diseases or conditions affecting the fetus primarily		39
Prematurity	38	
Quinin poisoning	1	
6. Cause unknown		28
Fetus at term		
	Total	199

This list includes 199 fetal deaths in which the primary cause was recognized as such, or as in the prematures, below twenty-eight weeks, or in the full-term infants, no primary maternal cause was noted in the records.

B. Under the causes and conditions in the mother associated with the fetal death are listed 16 groups of diseases or conditions which closely follow the groupings of the International List of the causes of death.

1. Infections		5
Influenza	1	
Tuberculosis	1	
Syphilis	3	
3. Endocrine and other general diseases		7
Diabetes	6	
Thyroid	1	
7. Disease of circulatory system		3
Diseases of heart	1	
Diseases of arteries	2	
8. Disease of respiratory system		1
Bronchitis	1	
9. Diseases of digestive system		2
Appendicitis	1	
Intestinal obstruction	1	
10. Diseases of genitourinary system		10
Known to have preceded pregnancy		
Nephritis	7	
Bicornuate uterus	1	
Fibromyomata uteri	2	
11. Diseases of pregnancy and childbirth		27
Sepsis—observed before delivery	1	
Albuminuria, eclampsia and pyelitis	12	
Other toxemias	1	
Hemorrhages (Placenta previa, 9)	12	
Rupture of uterus	1	
13. Conditions of bones interfering with normal labor		1
Fracture of dorsal spine	1	

This group of conditions, 56 in number, comprises some reduplications in the groups on toxemias and hemorrhages.

the minute details of the situation, to ascribe the fetal death to drugs or anesthetic agents. Such obscure cases must be discussed early when all the unwritten but observed data can be freshly reviewed for an impartial decision. This is a function of hospital obstetric staff conference. Such deaths as might have been due to sedative drugs or anesthetic agents therefore have been ascribed to the "no cause given" group. The uterine stimulating agents, derivatives of the pituitary gland, have been so sparingly used during labor that they can be ruled out as causes of fetal death in this series.

There were 66, or 30 per cent, macerated fetuses in this series, 24 from the twentieth to the twenty-seventh week, 19 from the twenty-eighth to the thirty-fifth week and 23 from the thirty-sixth to fortieth week or over. Of these macerated fetuses, 46, or 72 per cent were autopsied. Even with this aid to diagnosis no cause was found for the fetal death in 15 cases. The various degrees of toxemia, including nephritis, accounted for 15 cases, cord difficulties for 4, diabetes for 3, hemorrhage conditions for 5, and antenatal fetal toxemia in intercurrent influenza for one, with other varied unit items. Maceration represents varying degrees of autolysis of the fetus; its extent depends upon the length of time the child has been dead, and may vary from maceration of the cutaneous surfaces only to such complete maceration of the entire body that the fetus appears as a sac of fluid. Although it is difficult to ascertain cause of death even by autopsy in the extreme degrees, maceration should be regarded only as an effect of the death and every effort made to determine the original cause. Strachan cautions regarding the x-ray picture of the long bones in macerated fetuses stating that maceration produces an appearance in the long bones quite similar to the osteo-enchondritis of syphilis.

AUTOPSY

We were fortunate in obtaining 132 autopsies, 57 per cent, in this series of 228 stillbirths. This figure is only slightly below the autopsy percentage of the general hospital deaths. Such examinations made definite the cause of death in a majority of the operative cases, particularly was it effective in demonstrating the effect of birth trauma upon the fetal cranial contents. In only four autopsies was an examination of the brain refused. The value of examination of this organ at autopsy as contrasted with a series of autopsies in which the brain was not examined is shown in the report of Fenton. In his first series of autopsies in which the brain was included, intracranial hemorrhage was shown to be the largest cause of death. In a second series where the brain was not examined, passive hyperemia, 33 per cent, led as a causative factor of death having increased from fifth place, 11 per cent, in the first series.

In many cases where at autopsy intracranial damage is so slight as to appear unlikely in having caused the fetal death, Holland ascribes the etiology to a traumatic cerebral asphyxia. A spinal tap showing bloody fluid immediately after birth of a freshly dead fetus often gives strongly suggestive evidence of a suspected intracranial hemorrhage. A routine x-ray of all freshly dead fetuses, at least of the head in forceps cases and the spinal column, in addition, in breech cases will often throw light on the cause of the death where autopsy is refused.

CAUSES OF DEATH

The causes of death in this series have been classified according to the causes of stillbirth given on the reverse of the proposed stillbirth certificate. These are divided into, (A) causes determined in the fetus and (B) causes and conditions

livebirths, Grade 3 had 63 per cent livebirths, and those with no care at all 58 per cent livebirths. Hence, he concludes, on a conservative estimate three-fourths of the 20 per cent antepartum period fetal mortalities could have been prevented by more efficient antenatal examination and care.

In a maternity hygiene program in Williamson County, Tennessee, the stillbirth rate in a supervised group, representing 42.8 per cent of the total reported births in the area studied was 16.2, over a period of six years. During these years the stillbirth rate for the unsupervised group, 41.8, and the state at large 44.9, were 2.6 and 2.8 times greater than that in the supervised group. On the other hand although only one-third of the women dying in association with stillbirths in the Philadelphia Mortality Study had received adequate prenatal care, inadequate prenatal care was regarded as an almost negligible avoidable factor in the death of the mother.

Our hospital standard of febrile morbidity is that accepted by many institutions, 100.2° F., twice in any one day or on consecutive days following the first twenty-four hours after delivery. Applying this standard the general average febrile morbidity of the hospital for several years has run slightly over 11 per cent, including extragenital as well as genital causes. In this series of 228 there was an associated febrile maternal morbidity in 43 cases, 18 per cent.

There were three maternal mortalities in this series of 228 women with stillbirths. Two women died of sepsis, one following an illegally induced interruption of pregnancy at the twenty-second week; one following a version and extraction; a third woman died of hemorrhage from placenta previa.

TABLE II. TIME OF FETAL DEATH IN RELATION TO LABOR AND OPERATION

		LABOR		OPERATION		NUMBER OF CASES	PER CENT OF DELIVERIES ASSOCIATED WITH STILLBIRTHS
		BEFORE	DURING	BEFORE	DURING		
Total	228	78	136			7895	Rate: 28.8
Spontaneous	127	62	51			4925	2.5
Operation	101	16	85	37	64	2970	3.4
Low Forceps	18	6	12	7	11	1908	0.9
Mid Forceps	20	2	18	5	15	618	3.2
High Forceps	11	1	10	1	10	40	27.0
Breech Extraction	16	3	13	4	12	110	14.5
Version	20	1	19	8	12	48	41.6
Cesarean Section	11	3	8	7	4	241	4.5
Craniotomy	5	0	5	5	0	5	100.0
Not Recorded	14						

SUMMARY

A stationary stillbirth rate demands more attention. Uniform statistical practices are desirable. The proposed standard certificate for stillbirth should hasten the adoption of uniform practice by states,

The group of fetal deaths listed under difficult labor, 62 in number, includes 42 cases of lacerations of the tentorium or falx, and various types of intracranial hemorrhages, as well as 3 cases of fractured skull, all parietal bone injuries, and one fracture of the cervical spine. The diagnosis of birth trauma in the sixteen remaining cases was either grossly evident or suggested by bloody fluid on spinal puncture.

The causes in this series show, as has been so often stated, that birth injury is one of the most important factors in the production of still-born infants. This group of deaths in large part must be ascribed to bad obstetries. The second largest group is made up of unexplained fetal deaths before the period of viability. Whether an intensive investigation of such premature stillbirth deliveries would throw light upon the etiology of this group remains an open question. Many of the case records in this group contain a notation that bleeding was noted at the onset of labor, yet they did not present the clear-cut clinical picture of premature separation of the placenta. Closely allied is the third largest group, stillbirths at term without a cause easily obtainable, from clinical record or autopsy, if one was performed. From the maternal standpoint, chronic renal lesions and toxemia play a large part, 34 per cent, with hemorrhages, 20 per cent, closely following them.

What part does senescence of the placenta, or placentosis as some obstetric pathologists term it, apart from the gross infarction common in the nephritis group, play in the group of deaths at term without any apparent cause. Certainly if we wish to exhaust all our resources in an investigation of such deaths we must consider the pathologic physiology of the placenta in the etiology. The studies of Goodall and others suggest such a condition as a premature senility of the placenta is a very likely factor not only in some of the unexplained stillbirths at term but also in the repeated or habitual death in utero just short of term.

There are two questions which arise in the management of a known dead fetus in utero. If the patient is not in labor, when and by what means is labor to be induced. In the majority of such cases labor occurs within a short time after fetal death. Dippel records retention of a dead fetus in utero for sixty-one days before expulsion occurred. Few systemic symptoms are noted in the average case.

The second question arises with the death of the fetus during labor. Aside from conditions which necessitate immediate delivery as placenta previa or other imperative situations under what circumstances should operative delivery be performed.

There is a definite relationship between the degree of antenatal care and the stillbirth rate. Brand states that 20 per cent of fetal deaths, collected observations, occur during the antepartum period. Analyzing the figures on antenatal care from the Fifteen States Survey, he shows that women who received Grade 1 or 2 prenatal care had 70 per cent

Coons and Blunt (1930) reported mineral balances on a number of pregnant women at various periods of gestation, revealing a positive calcium balance in nearly all cases, but the amount of calcium varied, the greater retention occurring toward the end of pregnancy. They found that the amount retained equalled only the estimated fetal requirements in 3 patients while in 6 it was decreased, thus indicating that these women were depositing only small amounts of calcium in the fetus or were using their own reserves to meet the fetal needs.

Baur, Aub and Albright cited by Madden (1933) advance the theory that calcium is stored in the trabeculae of bones in readily available and sufficient quantities for fetal use. Madden states that the fetus in utero rarely, if ever, suffers from the lack of calcium, and it is extremely doubtful if prenatal rickets ever occurs. Bernheim (1933) states that there is a large supply of calcium present in the maternal bones and this store can be drawn upon over a considerable period of time without producing obvious osteoporosis or a reduced content of the blood.

Mull and Bill (1932), from a review of the literature, found that there still exists a wide diversity of opinion as to what changes in the serum calcium if any, actually occur during pregnancy. Investigators accept a range of 9 to 11 mg. per hundred c.c. as the normal total serum calcium concentration and 3.7 mg. per hundred c.c. for the inorganic serum phosphorous in the blood. Morley (1913) reported a lowering of the serum calcium during late pregnancy, labor, and the puerperium. Widdows (1923) followed individual cases over an extended period of time and concluded that there was a tendency toward a decrease in the calcium content of the blood in late pregnancy which was not manifest in all cases. Cantarow, Montgomery, and Bolton (1930) summed up the literature with the conclusion that the total serum calcium diminishes during the later months of pregnancy, but is usually above the lower limits of normal. They attributed symptoms of calcium deficiency to variations in the diffusible and nondiffusible forms. Andersen and Oberst as late as 1936 studied the diffusible and nondiffusible calcium in pregnancy and concluded that the average values for these forms are fairly constant irrespective of pregnancy, and that the reported variations are due primarily to changes in the total calcium.

In regard to the calcium concentration in the fetal blood there is entire agreement. Serdyukov and Morosova, Boek and Bokelman, and Hellmuth all found the fetal concentration definitely higher than the maternal, the first named to the extent of about 20 per cent.

Sherman (1931) considers 0.45 gm. of calcium per day as the actual body requirements, but for safety, this minimum for an adult should be increased to 0.75 gm. per day. During pregnancy, however, the calcium requirements of women are greatly increased especially in the last trimester, and it is estimated that 1.6 gm. per day are the optimum requirements. The physiologic need for phosphorous has been shown to be 1.5 to 2 gm.

That the calcium and phosphorus metabolism is influenced by many factors has been pointed out by various observers; thus the source, the presence or absence of unfavorable elements simultaneously ingested which may unite to form insoluble salts, the hydrogen ion concentration in the stomach and small intestine, the activity of the parathyroid glands, vitamin D, and possibly vitamins A and C.

There are many forms of calcium on the market. Dicalcium-phosphate is said to be an excellent source, particularly because the calcium and phosphorous are present in approximately the same relationship as that found in bone.

cities and clinics. The Children's Bureau study should be assisted. Similar city wide studies might be desirable. Local studies in individual hospitals would encourage better obstetrical practice both in the antepartum and intrapartum periods to the benefit of the fetus.

In this series of 228 fetal mortalities birth trauma is again shown to be the largest single factor in the etiology. There is a large group of unexplained stillbirths, in both viable and previable fetuses. More intensive studies of fetus at autopsy, placenta by histology and mother or parents by clinical investigations should solve some of these deaths. From the maternal aspect, the toxemias, nephritis and hemorrhages are the principal causative factors.

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BONE CHANGES IN THE FETUS FOLLOWING THE ADMINISTRATION OF DICALCIUM-PHOSPHATE AND VIOSTEROL TO THE PREGNANT MOTHER*

GEORGE C. FINOLA, M.D., RUTH A. TRUMP, B.S., AND
MOZELLE GRIMSON, B.S., CHICAGO, ILL.

(From the Department of Obstetrics and Gynecology, Northwestern University and
St. Luke's Hospital)

A SURVEY of the literature reveals a paucity of information upon the subject of bone changes in the fetus following the administration of calcium, phosphorus, and vitamin D to the pregnant mother.

Romaniello (1933) in a small series of 8 controlled cases, reports an increased bone density, smaller fontanels, narrower sutures and an increased birth weight in those babies whose mothers had been subjected to moderate doses of vitamins during pregnancy. Booher and Hansmann (1931) studied calcification of the tibia in 8 normal dead newborn (delivery accidents) and found that the calcium content varied slightly despite large doses of calcium, phosphorus, and vitamin D ingested. Coons and Blunt (1930) in an equally small series state that x-ray studies of the wrists and ankles of the newborn showed a tendency toward cupping in the distal ends of the ulna, flattening of the ends of the other long bones, and poor calcification of the epiphyseal ends of the diaphyses paralleling the bad calcium and phosphorus retention of the mothers.

Schmitz (1931), Fehling (1877), Mielch (1899), Hugouneng (1900), and others analyzed the mineral content of the aborted fetus at various periods of gestation and while these figures varied, in general it may be said that the fetal content increased many times in the last three months of pregnancy.

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TABLE I. CONTROLS. BLOOD CHEMISTRY

	1 MO.		2 MO.		3 MO.		4 MO.		5 MO.		6 MO.		7 MO.		8 MO.		OVER-DUE 9 MO.		DELIVERY		CORD BLOOD	
	CAL.	PHOS.	CAL.	PHOS.	CAL.	PHOS.	CAL.	PHOS.	CAL.	PHOS.	CAL.	PHOS.	CAL.	PHOS.	CAL.	PHOS.	CAL.	PHOS.	CAL.	PHOS.	CAL.	PHOS.
T. B.					9.80	4.30	10.24	3.90	9.30	3.84	10.25	3.80							10.35	4.06	11.80	7.20
B. N.					9.70	3.04	10.35	3.00														
P. B.					10.20	3.70	10.50	4.07	10.00	3.50	10.00	3.50							10.00	4.10	11.86	5.21
C. A.					10.30	3.76																
F. J.																						
A. B.			10.10	3.60																		
H. R.					10.00	2.90			9.00	3.19												
M. R.									9.80	3.80												
A. T.																						
C. N.					9.70	3.26													9.75	3.86	10.55	
C. C.																					11.00	
C. R.					10.45	3.58			9.85	3.66									9.70	3.60	11.56	3.60
D. S.					10.40	3.56			10.50	3.58									9.06	3.00	11.41	4.10
E. N.					10.30	3.30																
A. S.																						
M. E.					9.80	3.74	10.00	3.64			10.50	3.74							8.94	2.98	10.88	4.10
G. B.					10.55	2.82	9.75	3.42			9.55	2.98							9.60	3.20	11.42	5.00
E. G.					9.85	3.30	10.31	3.54			9.90	3.65							9.70	3.98	11.50	6.42
F. P.																						
A. C.											10.00	3.04							10.65	3.86	12.20	8.10

Prem. Twins

In the present investigation 75 women at various stages of pregnancy were selected for observation. Seventeen of these were later dropped for lack of cooperation. Thirty-three were used for treatment and 25 with approximately the same weight, gravidity and expected date of confinement served as controls.

All of the patients were instructed on the so-called basic pregnancy diet which contains 1.5 to 1.85 gm. of calcium and 1.5 to 2 gm. of phosphorus per day, and each was requested to return weekly reports of

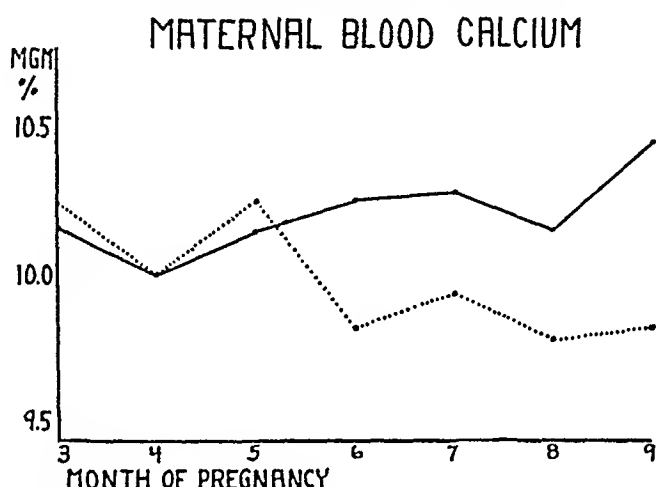


Chart 1.— ——— Treated group. Controls.

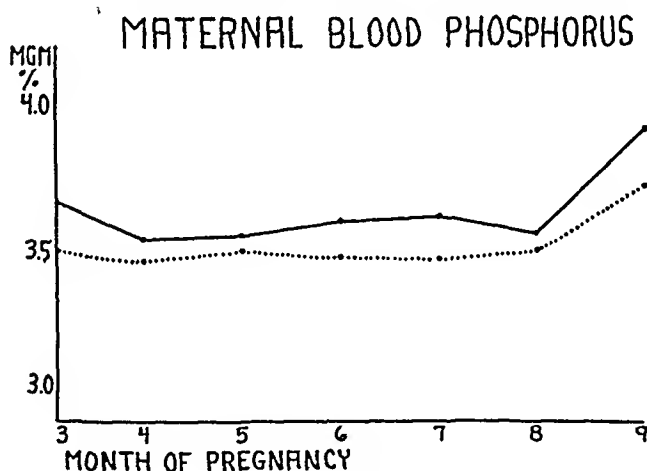


Chart 2.— ——— Treated group. Controls.

all foods, together with the quantity consumed between visits. To those in the treated group, the diet was supplemented by dicalcium-phosphate (dulcet bars) in doses of 6 segments (1.44 gm. calcium, 1.08 gm. phosphorus), and 30 drops of viosterol (250 D) per day. To assure ourselves that the amount prescribed conformed with the quantity actually taken, they were requested to return their boxes at fortnightly intervals so that all bars could be recorded or accounted for and a fresh supply re-issued.

Blood samples for calcium and phosphorus determinations were obtained from each patient upon her first visit, and subsequently at

TABLE II. DI CALCIUM-PHOSPHATE VIOSTEROL GROUP, BLOOD CHEMISTRY

	1 MO.		2 MO.		3 MO.		4 MO.		5 MO.		6 MO.		7 MO.		8 MO.		9 MO.		DELIVERY		CORD BLOOD	
	CAL.	PHOS.	CAL.	PHOS.	CAL.	PHOS.	CAL.	PHOS.	CAL.	PHOS.	CAL.	PHOS.	CAL.	PHOS.	CAL.	PHOS.	CAL.	PHOS.	CAL.	PHOS.	CAL.	PHOS.
M. De.																						
S. M.									10.00	4.13	10.00	3.58	9.40	3.58	10.25	3.60			9.56	2.50	10.88	4.10
R. D.									9.80	4.00	9.80	3.16	10.50	3.48	10.65	3.44			10.37	3.30	11.25	9.10
V. D.									10.30	4.10	10.30	4.10	10.55	4.00	10.69	3.84			10.55	2.86	12.85	4.14
L. M.									9.75		9.75	3.10	10.30	3.00	10.90	3.86			9.36	3.22	12.05	5.20
M. B.									10.85	3.00	10.85	4.22	10.10	3.56					10.50	4.30	11.40	6.88
H. L.									10.80	4.00	10.15	4.00	9.51	3.20	9.85	3.18			10.70	4.12	11.80	5.28
E. H.									9.45	3.50	10.70	3.96	10.65	3.96	10.00	3.96			11.55	4.46	11.70	6.20
E. E.									10.90	3.80	10.60	3.73	11.45	5.32	10.80	4.64			10.20	4.00	12.35	4.00
A. L.									9.60	3.18	9.90	3.20	10.35	3.82	10.00	3.52			10.80	4.20	12.80	6.20
C. U.									9.85	3.42	9.85	3.54	10.49	3.78	10.15	3.90						
M. W.									10.40	3.40	9.85	3.28	10.30	3.36	10.05	3.44			11.75	4.30	13.00	5.86
M. S.									10.70	3.44	10.70	3.78	10.40	2.88	9.10	3.26			11.05	4.20	12.05	11.20
E. H.									10.85	3.30	10.85	4.32	9.60	4.20	10.75	3.36	10.50	2.96	10.80	4.50	13.00	9.86
C. S.									9.85	3.42		2.80	10.50	3.96	9.65	3.52			9.68	3.97	12.27	5.56
D. L.									10.00	4.06		3.66	10.27	4.20	10.29	3.12			9.30	3.35	10.20	7.00
G. J.									11.45	4.06		4.96	10.45	3.70	10.35	3.74			10.40	3.70	11.84	4.96
A. M. J.									10.24	3.84	10.24	3.84	10.65	3.40	10.60	4.28	10.60	3.42	11.00	3.52	11.80	5.60
A. K.									10.35	3.72	9.74	3.62	10.65	3.00	10.58	3.44				3.44		5.96
A. E.									10.10	3.18	10.05	3.18		3.00		3.86	11.00	3.90	10.30	4.10	10.50	3.54
																Prem. Twins						
M. C.									9.64	3.68	9.40	3.46	9.25	3.60	9.25	3.26			9.85	5.40	11.85	3.68
M. A.									11.10	3.66	10.23	3.62	10.35	3.44	9.50	3.56			10.64	3.26	12.75	6.00
A. M.									10.05	3.04	10.45	3.04	9.25	3.04	9.50	3.14			9.35	3.80	12.65	5.52
R. W.											11.70	2.80			10.50	3.04			9.85	4.68	11.95	7.54
C. H.													9.76	3.44	10.30	3.74			10.00	4.46	11.00	5.60
L. H.									9.60			3.20			10.45	3.36						6.94
I. S.									10.25	3.66		3.30	8.80	3.14	9.25	3.72			9.50	3.55	11.00	5.80
B. L.									9.70		9.70	4.40	10.00	2.76	9.40	3.42			10.72	4.26	11.75	8.36
L. S.											10.55	2.96	11.00	3.62	11.20	2.90			9.85	2.64	11.85	5.20
F. S.													10.40	2.66	10.00	3.40	10.90	3.44	12.30	4.30	13.00	5.80
M. G.									11.05	3.49	11.05	3.54	11.00	3.66	8.95	2.66			10.58	3.65	11.90	5.60
M. P.									11.20	3.68	11.20	3.46	10.50	3.42	10.00	2.70			10.00	2.90	11.90	4.92
N. A.									11.20	3.42	11.20	4.06	11.28	4.00	10.00	3.42			10.00	4.30	11.35	7.54
Average									10.25	3.55	10.25	3.60	10.28	3.61	10.17	3.55			10.44	3.92	12.11	6.15

TABLE I—CONT'D

	1 MO.		2 MO.		3 MO.		4 MO.		5 MO.		6 MO.		7 MO.		8 MO.		OVER-DUE 9 MO.		DELIVERY		CORD BLOOD	
	CAL.	PHOS.	CAL.	PHOS.	CAL.	PHOS.	CAL.	PHOS.	CAL.	PHOS.	CAL.	PHOS.	CAL.	PHOS.	CAL.	PHOS.	CAL.	PHOS.	CAL.	PHOS.	CAL.	PHOS.
S.S.					11.80	3.18	9.60	3.75														
A.C.					10.40	3.46	9.85	3.34														
H.B.					10.55	2.66																
F.L.					11.10	3.66																
M.M.					8.92	3.72			9.74	3.68	9.40	3.10										
J.M.					10.50	2.94			10.50	2.94												
J.W.					8.90	3.12																
B.T.					10.05	3.04			10.90	3.52	9.80	3.54	9.80	3.96					9.80	3.80	11.74	4.00
M.B.									10.53	3.72												
T.M.					10.80	3.32	10.00	3.14					10.00	3.10	9.96	3.12			10.60	3.96	12.06	5.68
C.S.	10.60	3.78	10.45	3.40			9.60	2.98			9.60	2.98	10.65	3.90	9.94	3.96			9.90	4.60	11.50	5.96
M.F.							9.80	3.54			9.80	3.54	9.50	3.60	9.80	3.58			10.60	6.06	11.30	9.60
G.W.					9.40	4.20					10.20	3.98	9.74	3.90	9.74	3.90			9.70	3.70	11.84	5.76
A.L.					9.55	4.12			9.55	4.12	9.35	3.62	11.05	3.04					10.10	3.44	11.75	5.66
M.D.					10.50	3.68			10.50	3.68	9.56	3.85	10.80	3.62	11.00	3.74			9.86	3.66	12.04	6.50
J.S.					10.50	3.20					10.40	3.00	9.60	3.20	9.05	3.10			10.10	3.56	11.80	5.42
M.Z.											9.89	3.26	10.00	3.64	9.76	3.24	10.20	3.40	10.30	3.72	11.30	4.80
H.R.					9.60	3.84					9.10	2.98	9.35	3.12	9.26	3.00			9.40	3.06	11.04	5.00
L.P.											8.90	3.20	8.70	3.46	8.50	2.96	8.50	3.50	8.46	3.00	10.50	4.60
R.M.											11.00	3.54	10.10	3.16	10.00	3.50			9.90	3.20	11.06	5.00
M.L.																						
Average	10.60	3.78	10.23	3.50	10.25	3.50	9.81	3.48	9.93	3.47	9.78	3.49	9.84	3.72	11.50	5.88						

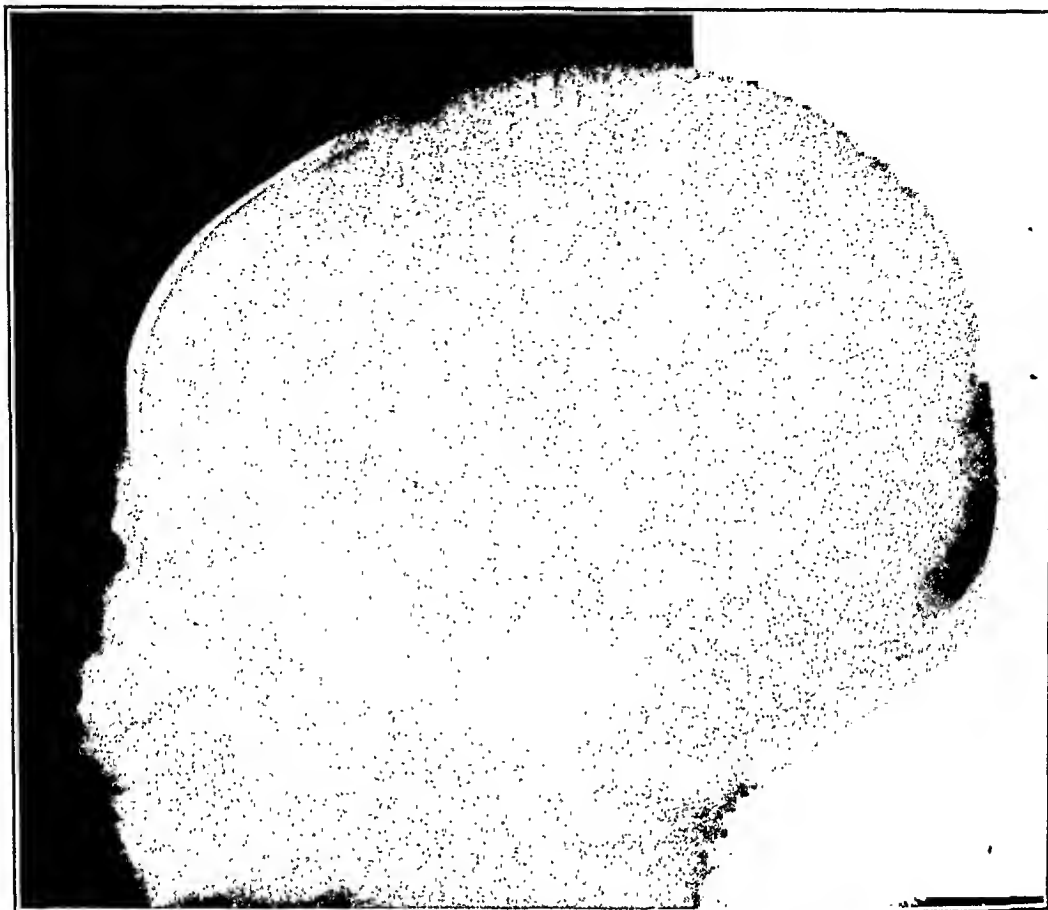


Fig. 2.—Showing hazy and indistinct upper border of parietal bone in control group offspring.

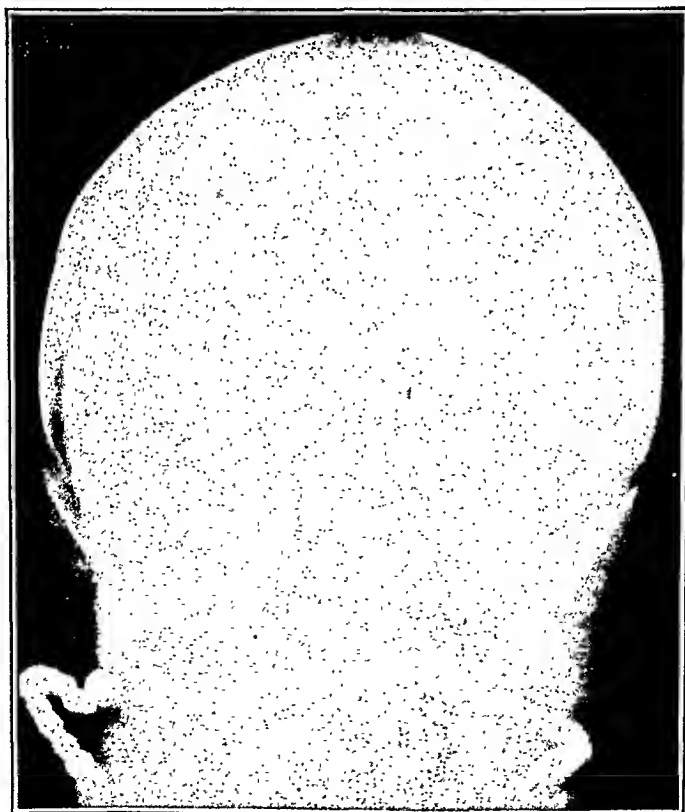


Fig. 3.—Control group showing width of fontanel.

monthly intervals throughout the pregnancy. Another sample was procured during the late first stage of labor, and cord blood was collected from the maternal end of the severed cord at birth. The total serum calcium determinations were made according to the Clark-Collip (1925) modification of the Kramer-Tisdall method, and the serum inorganic phosphorous by the method of Kuttner and Lichtenstein, applying the correction for deviation from Beers Law as determined by Bodansky.



Fig. 1.—Illustrating average bone density of ribs and epiphyses at the knee in the control group.

Some twelve to thirty-six hours after birth, roentgenograms were taken of each infant in the anteroposterior and lateral views of the skull, and the anteroposterior view of the trunk and extremities, using the same technique in all.

In Tables I and II are listed 670 consecutive total serum calcium and inorganic phosphorous estimations. Some of these patients it will be observed were dropped after one or more determinations and a few are undelivered at the time of this report. Several significant facts however

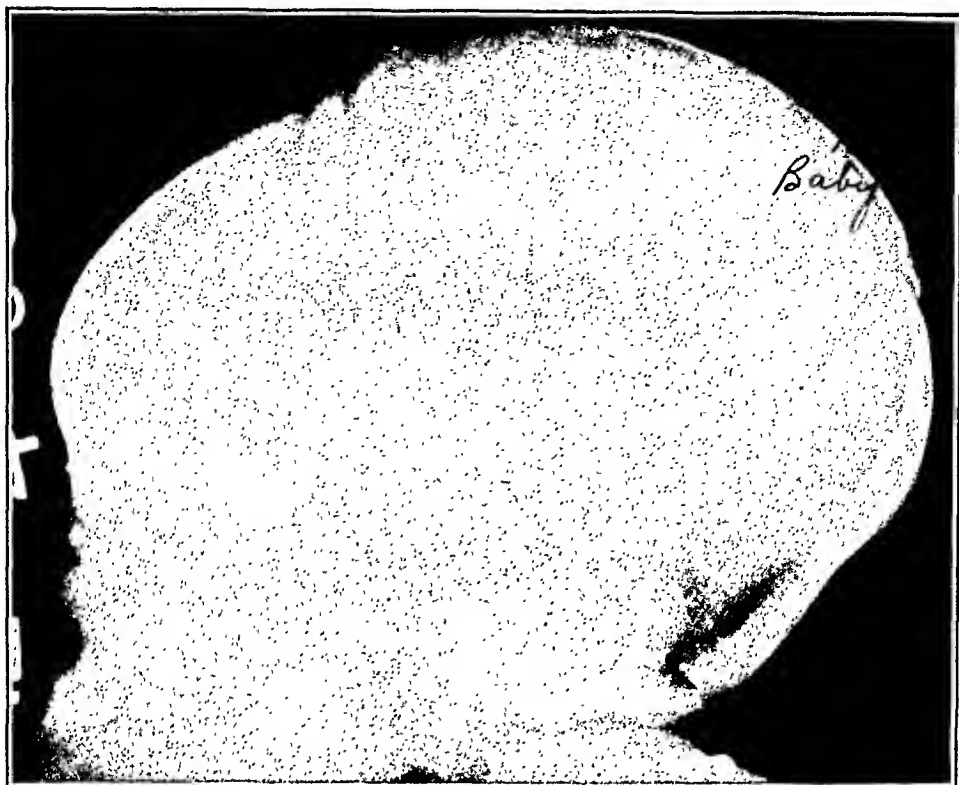


Fig. 5.—Showing sharply demarcated upper border of parietal bone in the treated group.

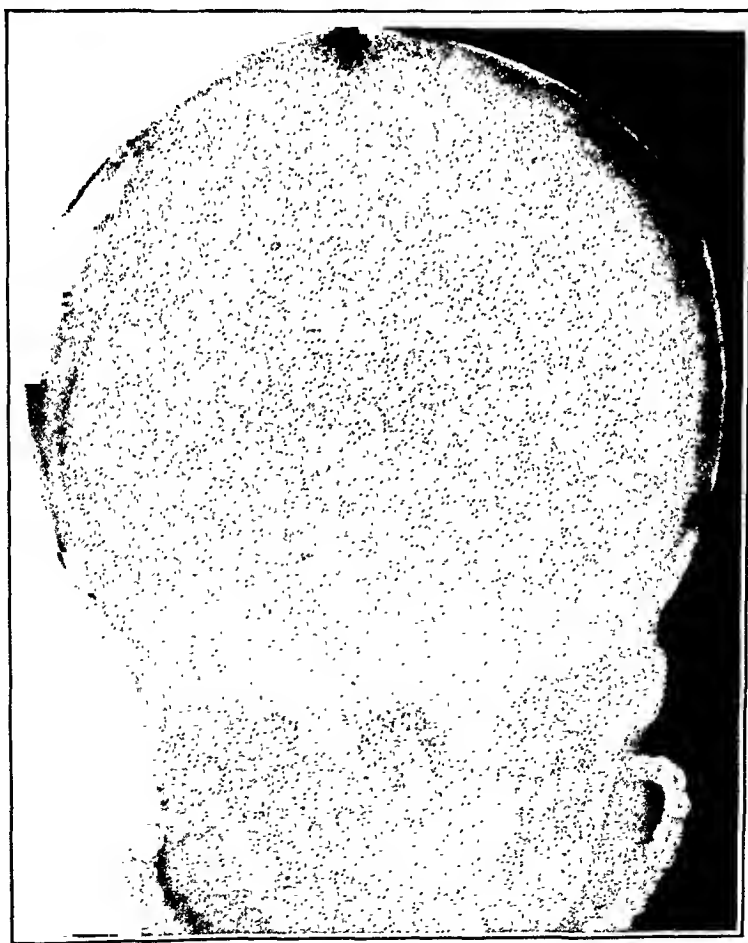


Fig. 6.—Treated group. Note size of fontanel.

do stand out: in the mothers of the control group there is a definite diminution of the serum calcium in the last trimester which is not apparent in the treated group; in the infants there is an increased calcium and phosphorous content of the blood over that of the mothers; and finally, these mineral levels are higher in the babies of the treated group than those of the control. Charts 1 and 2 illustrate these findings in graphic form.



Fig. 4.—Treated group, illustrating increased density of the ribs, and increased size and density of epiphyses at the knee.

Figs. 1 to 9, selected as representative of each group, demonstrate clearly the marked tendency in the treated group's offspring toward increased bone density, especially in the ribs, the parietal bones, and the epiphyses of the long bones at the knee. The x-ray films were interpreted by Dr. E. L. Jenkinson of the Department of Radiology at St. Luke's Hospital. The ribs can be seen to stand out clearly and distinctly in the treated group, the epiphyses about the knee are larger and more dense, and of even more significance, the upper borders of the parietal bones are clear and sharply demarcated, while the ribs,

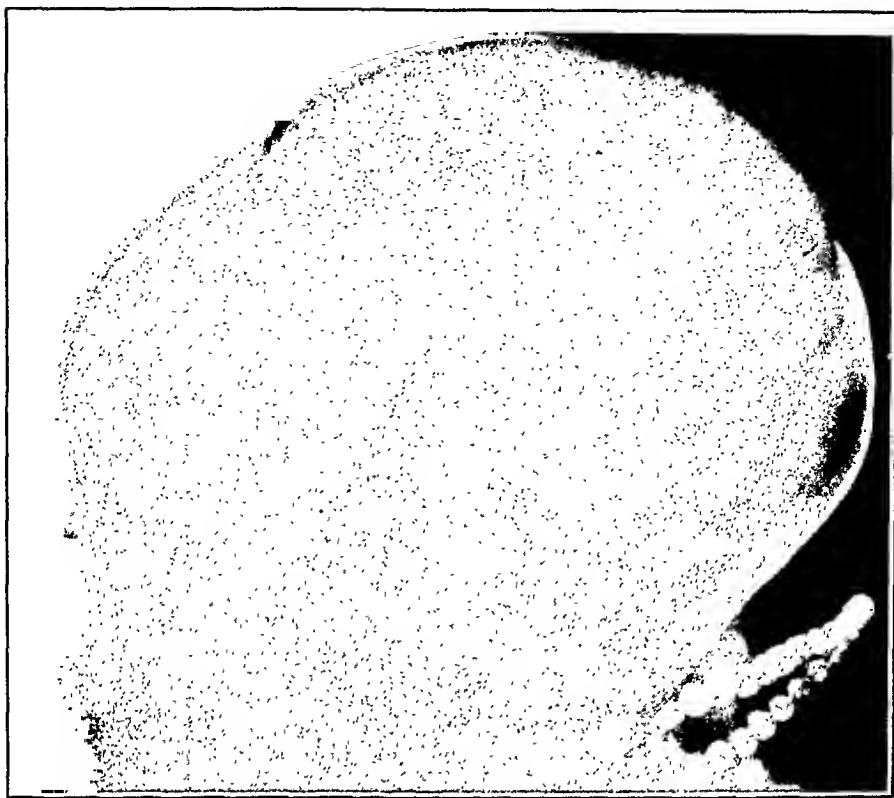


Fig. 8.—Treated group showing dense line of demarcation at upper border of parietal bone.

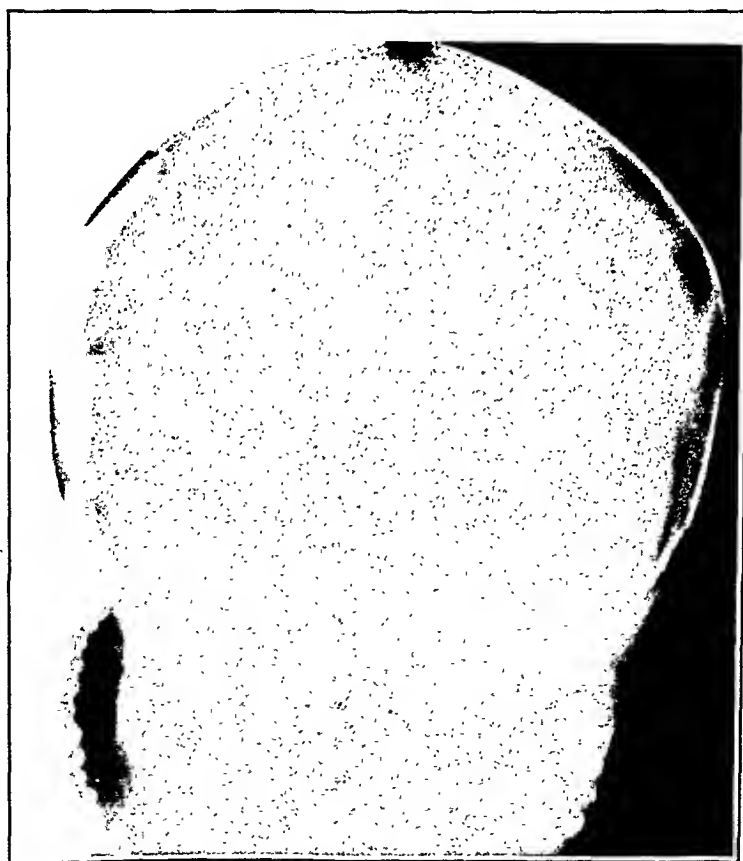


Fig. 9.—Treated group. Note size of fontanel.

epiphyses, and parietal bones in the controls are hazy and indistinct. Some unexplained variations from these results occurred as follows: 15 per cent of the mothers who seemed to have taken their medication conscientiously, showed fetal x-rays which compare only equal in bone density to that of the normal controls. Several controls showed diminished calcification below that of the average control. Only one control showed calcification equal to some of the lesser marked bone changes in the treated group.



Fig. 7.—Treated group showing slight increase in size and density of epiphyses at the knee.

The average width of the fontanels, as measured from the x-ray films, was 4.6 mm. in the treated group as against 6.4 mm. in the control group. A word of caution in the interpretation of the measurements of the fontanels seems justified; many of these babies were x-rayed before the normal contour of the head, deformed by molding, had been restored, so that comparison in this series did not seem entirely reliable.

The average weight of the infant in the treated group was found to

DISCUSSION

DR. JAMES E. FITZGERALD.—It is very interesting that a definite change in the bony structure of the fetus can be brought about by dicalcium-phosphate and viosterol. Yet like other things that are presented to us, we do not know what to do with this information. Neither the pediatricians nor ourselves know enough about newborn babies to know whether we are doing harm or not by such treatment. The answer will depend entirely upon some one's determining what is a perfectly normal baby and whether babies with denser skulls are better babies than the ones whose skulls are not so dense.

I would like to ask Dr. Finola whether it is possible that the increase in blood volume in the later months of pregnancy would account for the decreased percentage of blood calcium. The blood may show a smaller number of milligrams of calcium per 100 c.c. because of the admitted increase in blood volume in these later months.

Too many of us prescribe medication of which we know very little. All of us have been giving calcium and viosterol probably more because of advertized suggestions than from a real knowledge of the results of this medication.

DR. FINOLA (closing).—I am unable to answer Dr. Fitzgerald's question regarding the cause of the diminution in blood calcium that occurs in the latter part of pregnancy in relation to the increase in blood volume.

A MODIFICATION OF THE LE FORT OPERATION FOR INCREASING ITS SCOPE*

J. R. GOODALL, M.D., AND R. M. H. POWER, M.D., MONTREAL, QUEBEC

THE LE FORT operation consists of a marsupialization of the vagina. Its chief application is found in cases of complete procidentia, where all supporting structures have been disrupted by the forceful descent of the hernia. This condition parallels the massive inguinal and abdominal hernias that one encounters in general surgery. In these cases, ectopic tissue has to be introduced from other parts of the body to make up the loss occasioned by the divulsion of the hernia. In massive procidentia of the genitals, marsupialization offers an easy, safe, and sure method of restoration. It has its very well-marked circumstantial restrictions, however. These are that the woman must be past the childbearing period; that she be a widow without prospects of remarriage. Its great advantages are that it is a relatively safe operation; that it can be done without spinal or general anesthesia; that the surgical risk is relatively slight; and that the results are uniformly excellent, even in the most senile cases, both generally and pelvically speaking. The greatest disadvantage of this operation lies in its restricted scope. Its greatest restricting circumstance lies in that a woman must be a widow in deed.

*Read at the Sixty-Second Annual Meeting of the American Gynecological Society, held at Swampscott, Mass., May 31 to June 2, 1937.

be 7 pounds and 6 ounces, that of the control 7 pounds and 7 ounces.

The average duration of labor was sixteen hours and thirteen minutes for the treated group as against fifteen hours and six minutes for the controls. The number of operative interferences was found to be: 2 midforeeps and 5 of the low variety in the treated group, 1 mid and 3 low in the control series.

There were no true dystocias encountered in either group but the number of cases in this investigation, we feel, is too small to warrant a definite statement as to the advisability of administering additional calcium, phosphorous, and vitamin D to the pregnant mother. However, it is reasonable to assume that with the increased density of the fetal bones, especially in the parietal region, molding which becomes an important factor in many borderline pelvises may be adversely affected, and it seems justifiable to warn against the indiscriminate use of large doses of both minerals and vitamin D during pregnancy.

SUMMARY

1. Fifty-eight women at various periods of gestation were studied during the remainder of their pregnancy. Thirty-three of these were treated with diacalcium-phosphate and viosterol while 25 served as controls.

2. The total serum calcium in the treated group increased slightly during the later part of pregnancy, while in the control group there was a definite diminution.

3. The total serum calcium and inorganic phosphorous of the newborn exceeds that of the mothers. This increase is more pronounced in the treated group.

4. There is definite evidence of increased bone density in the majority of infants born to the mothers of the treated group. The sites of predilection for this increased density were found to be: in the ribs, in the parietal bones and in the epiphyses at the knee.

5. It is suggested that this osteosclerosis, especially in the parietal region, might possibly interfere with molding of the head which is so often a very important factor in many borderline cases.

These preparations were generously donated by the Abbott Laboratories, Chicago.

III.

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the bases of the two triangles together by a continuous chromic catgut suture. This first step closes off the cervix (Fig. 2) from view, and establishes the crossbar of the vagina, by which the cervix communicates with both vaginas now in the process of formation. To approximate the rest of the denuded triangles, a single suture is passed from the posterior vaginal wall a quarter of an inch outside the margin of denudation, and about one-third inch down the vagina from the basal suture, and either undermines or pliates the raw surface of the posterior triangle to its midline. The suture now picks up a corresponding point in the midline of the anterior denudation, undermines it or pliicates it, eventually to emerge on the anterior vaginal wall, one-fourth of an inch from the raw surface (Fig. 3). It will depend



Fig. 3.—Position of the sutures for the co-aptation of the anterior and posterior denuded raw surfaces.

upon the thickness of the tissues, denoting the proximity of bladder on the anterior wall, and peritoneum on the posterior, whether one undermines or pliicates. A similar suture is introduced on the opposite side. These two are now tied, just tightly enough to approximate, but not to strangle the tissues. Similarly placed sutures are continued down each side, each about one-third inch apart, until the apices of the denuded triangles are closed, the one over the other. The final result is a double vagina, beginning with the vulva and communicating above by a cross-bar below the cervix. The knots are all exposed in the double vaginal canals, and a minimum of catgut is buried to be digested—a matter of considerable importance in senile cases. The vast majority of these cases are of this age. There is no age limit to this operation. It can be done under scopolamine and morphine, and if the marsupialization is followed by a perineorrhaphy, local anesthesia of the vulva is simple and effective.

The present modification removes this second disadvantage. It is but necessary that a woman be past the menopause, or be rendered sterile at the time of operation.

The modification here outlined may or may not be preceded by a vaginal hysterectomy. This antecedent procedure will materially depend upon the healthy state, or lack of it, of the upper genital organs. The Le Fort, when preceded by a vaginal hysterectomy, must undergo a slight modification of minor importance.

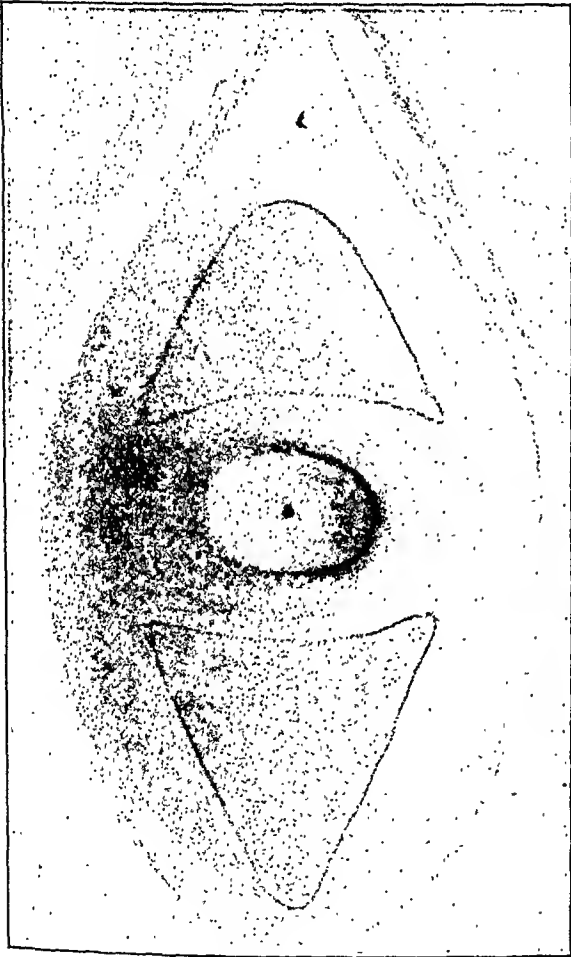


Fig. 1.

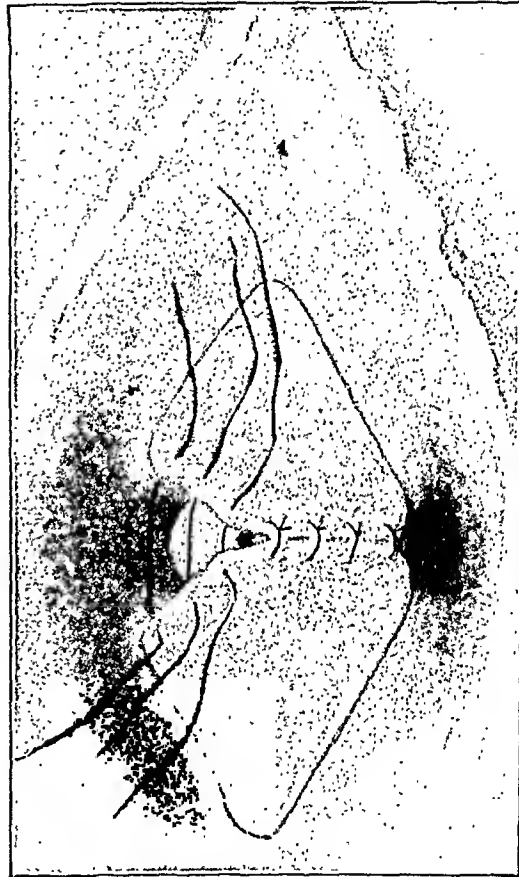


Fig. 2.

Fig. 1.—First procedure in modification of the Le Fort operation. Denudation of anterior and posterior wall in uncomplicated cases.

Fig. 2.—Suture of the bases of the denuded triangles. The right half of the cervix and external os still visible in the unclosed half.

The Le Fort as described by its author, and as presently put into practice, consists in a denudation of a long narrow triangle on the posterior wall of the vagina, and a similar one on the anterior. These denuded areas have their base near the cervix, and their acute angle near the vulva (Fig. 1). The bases of the denuded triangles in the anterior and posterior fornices should be far enough from the cervix, anteriorly and posteriorly, to permit free drainage of the cervical and uterine secretions down either of the two vaginas. The operation is completed by the complete approximation by sutures, of the anterior and posterior vaginal denudations. The suturing, as practiced by Le Fort and by the late Professor William Gardner, consisted in sewing

The modification about to be described, consists of a similar marsupialization of the vagina,¹ but the base is made narrow or wide, depending upon the vaginal capacity, and² the apex of the marsupialization should extend down the anterior or posterior walls various distances, depending on the length of the vaginal cavity. As a rule, the marsupialization involves only the upper third of the vaginal long axis. Before the two apices are sutured together, the anterior vaginal wall below the anterior apex is opened up as in an ordinary cystocele operation, with dimensions of denudation proportionate to the size of the cystocele (Fig. 4). This is then closed by its fascial layers, and when these deep layers are closed, the marsupializing

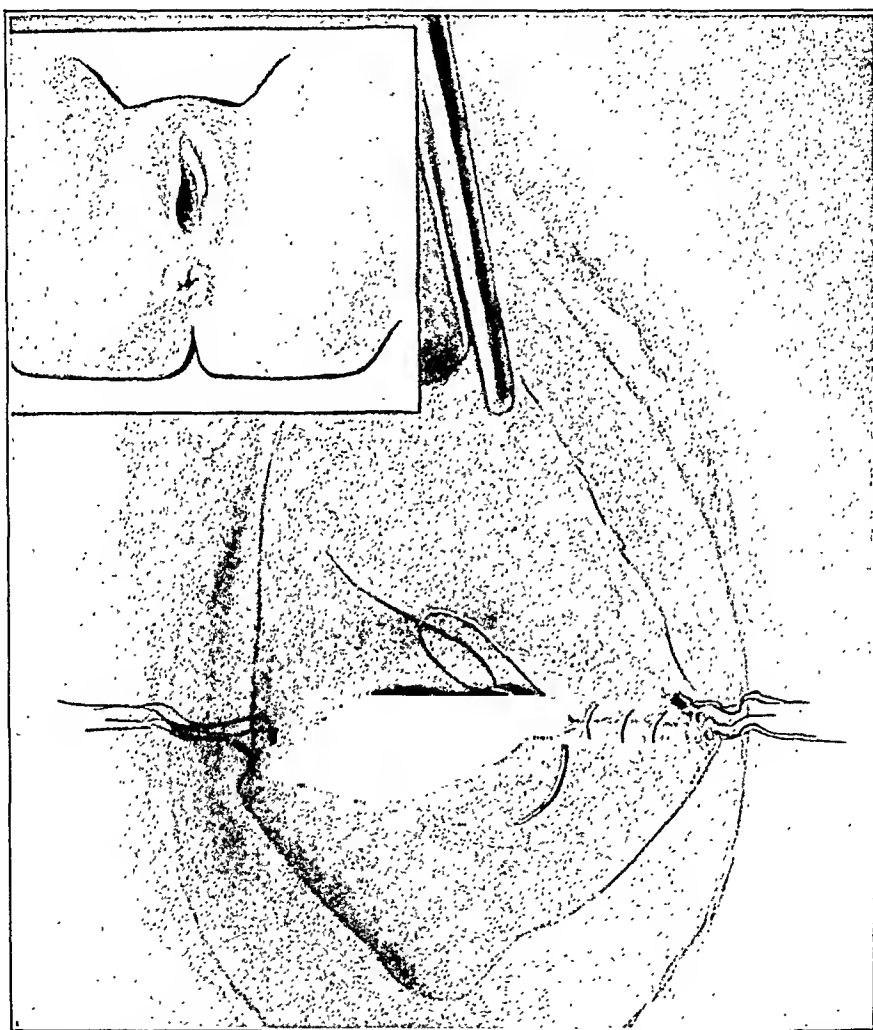


Fig. 6.—Approximation by suturing of the vesical peritoneum to the posterior parietal peritoneum, after vaginal hysterectomy. Small diagram shows the position of the patient.

sutures are continued to the posterior apex, and the mucosa of the anterior colporrhaphy is then closed. The last step of the operation consists of an extensive perineorrhaphy, the upper apex of which usually extends into the sides of (Fig. 5) the apex of the posterior marsupialization. The resultant is a single vagina for about two-thirds of the vaginal long axis, and a double vagina of the upper one-third of its length. The upper marsupialization gives the patient an irreducible fixation point to which the anterior colporrhaphy and perineorrhaphy are dependent. The end-result is surprisingly effective. I have performed the operation 24 times with uniformly satisfying results. Chromic twenty-day No. 0 catgut was used

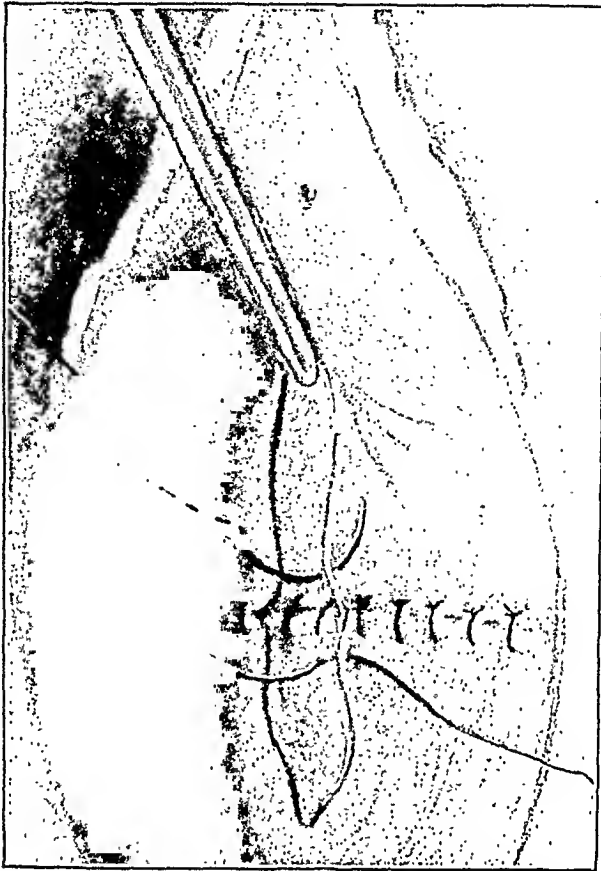


Fig. 4.—The vaults of the vagina have been closed and co-aptation of the denuded surfaces is being completed.



Fig. 5.—The anterior colporrhaphy has been completed below the marsupialization and the mucosa of the posterior wall is being approximated after co-aptation of the fascial layers. The further denudation for the perineorrhaphy is outlined in red.

and denudes a strip along the whole length of the posterior wall, from about the junction of its lower and middle third up to the raw surface of the primary circumcervical incision. The denuded areas, anteriorly and posteriorly, are now continuous with each other and with the open bases of the broad ligaments (Fig. 7). One now begins to suture. With forceps placed at each lateral end of the primary incision in the right and left fornices, one sutures the anterior margin to the posterior with a series of interrupted No. 0 twenty-day chromic catgut sutures, until the bases

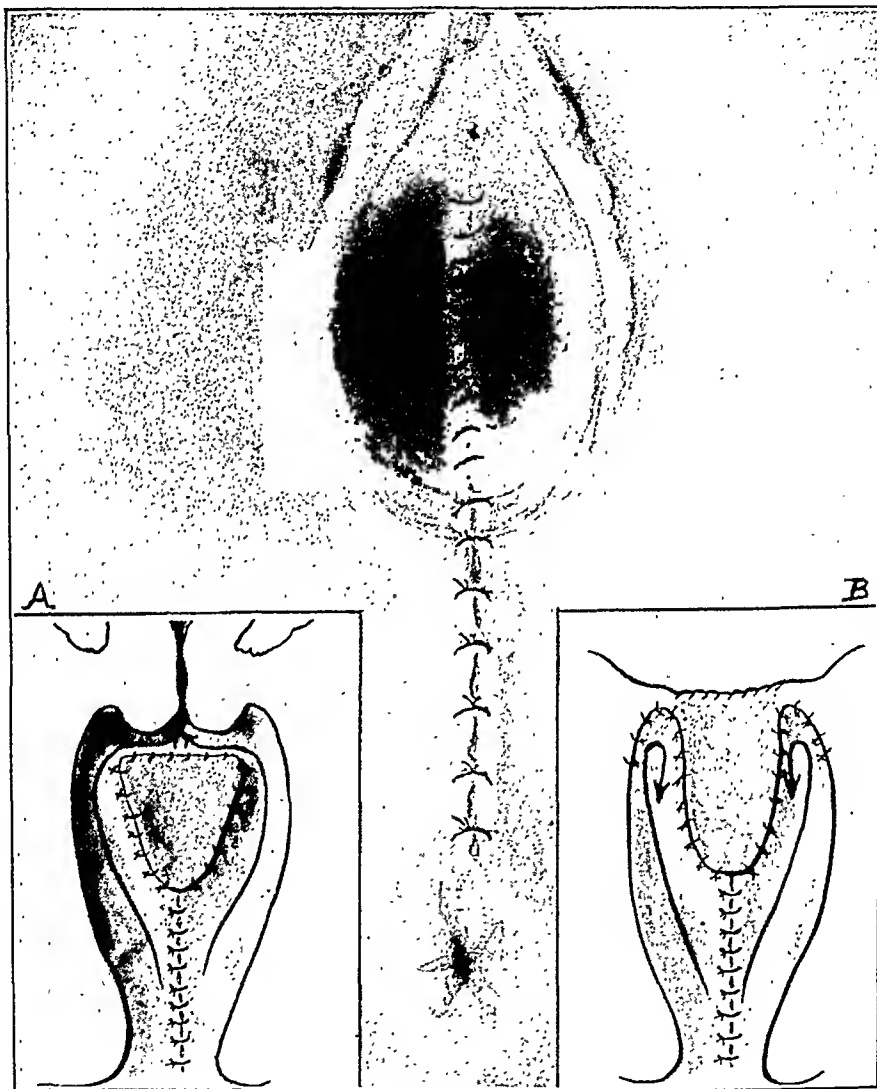


Fig. 9.—Completed appearance of the modified Le Fort, showing sutures of the anterior colporrhaphy and the extensive perineorrhaphy. The apex of the marsupialization is visible in the midline, high up in the vagina with the recesses of the double vagina visible on either side. *Inset A*, Appearance of lateral section with the completed operation where hysterectomy was not done. *Inset B*, The appearance of a similar section after vaginal hysterectomy.

of the marsupial denudation is reached on either side (Fig. 7). The further suturing is continued as described above, in the uncomplicated cases (that is, without preliminary vaginal hysterectomy).

The end-result in the complicated cases is a single vagina for the lower two-thirds of the long axis of the vagina, and a double vagina for the upper third. But they differ from the uncomplicated cases in that there is no subcervical crossbar to unite the vaginas. They end in blind culdesacs (Fig. 9).

throughout. The healing was eminently satisfactory, and there was uniform subjective satisfaction, except one case of dyspareunia due to too effective closure of the vagina. This was one of the first of the series. The ages varied from fifty-six to seventy-four years.

The modification, above described, may be immediately preceded by a vaginal hysterectomy. Under these circumstances, the technique is slightly different in its initial stages. After removal of the uterus, the anterior (vesical) peritoneum is sutured to the posterior peritoneum of the Douglas pouch by a continuous No. 1 plain catgut (Fig. 6). The suture should transfix the upper apices of the broad ligaments. The two broad ligaments are now brought together by a continuous suture

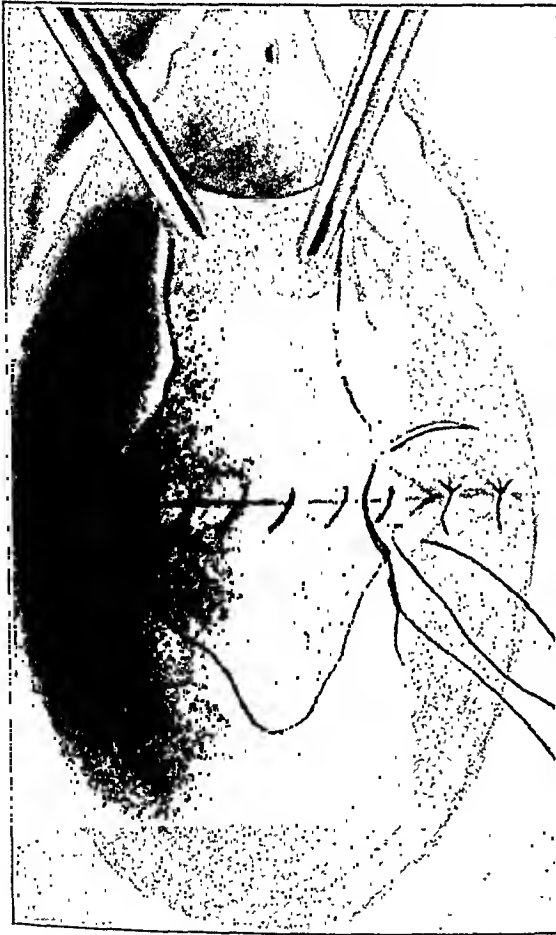


Fig. 7.

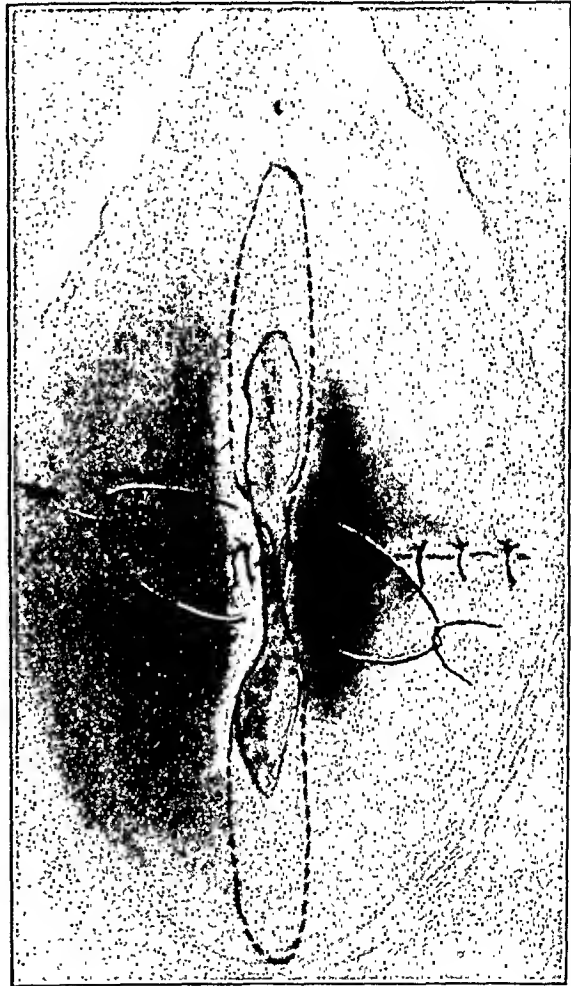


Fig. 8.

Fig. 7.—After closure of all anterior and posterior raw surfaces to eliminate dead spaces following hysterectomy, the vaginal vault is being closed with interrupted sutures and denudation of anterior and posterior vaginal walls is shown, constituting the first step of the modified Le Fort.

Fig. 8.—Co-aptation of raw surfaces and dotted outline of further denudation to constitute anterior colporrhaphy and posteriorly denudation becomes continuous with an extensive perineorrhaphy.

right down to, but not involving, the anterior and posterior vaginal incisions, so that no dead space is left in the pelvic raw surfaces (Fig. 7). One now proceeds with the marsupialization. From the anterior margin of the incision, the anterior vaginal mucosa is denuded down to the external meatus as in an ordinary anterior colporrhaphy. The upper part of the denudation seldom exceeds one inch in width, but it broadens out at the widest part of the cystocele to proportions adequate to the size of the cystocele (Fig. 8). One now picks up the posterior incision in the vault,

I see a case where I could utilize this modification. In some of the cases Dr. Goodall has reported, I would, however, have chosen to do an interposition operation with sterilization.

I know of no other surgical procedure which cures so much pathology with so little surgical risk. One of my former residents did a Le Fort operation on a patient about sixty-three years of age who had complete prolapsus. The result was so excellent that the patient's widowed mother, a woman of ninety-three years, who also had a complete prolapse, insisted that the operation be performed on her. This old lady was operated upon under morphine and scopolamine anesthesia with an excellent result and lived in greater comfort to be almost one hundred years old.

DR. JOSEPH L. BAER, CHICAGO, ILL.—We are well aware of the fact that the supporting structures in the region of the upper third of the vagina anteriorly and posteriorly are comparatively feeble. Apparently therefore the cure that Dr. Goodall obtains by approximating only the upper third of the vagina, anteriorly and posteriorly, is dependent rather largely on his reconstruction of the vaginal tube in its distal two-thirds. The reconstructed pelvic floor apparently is the chief support of the prolapsed uterus which has been pushed up and held above the approximated anteroposterior upper third of the vagina. This to a certain extent substantiates the view of those who believe that prolapse can be cured solely by simple vaginal reconstruction. This is a view to which I do not subscribe.

DR. JAMES R. GOODALL, MONTREAL, QUE. (closing).—These 24 cases to which I had alluded were cases where marital relations might take place afterward. Their ages varied from fifty-six to seventy-six years. It was with the idea of overcoming the restriction of the Le Fort operation to patients not requiring the retention of the capacity for future intercourse that this modification was primarily instituted.

Many of these patients had conditions which made them rather serious risks—glycosuria, high blood pressure, and other difficulties. Some of these can be overcome prior to operation. One thing which I think deserves a great deal of attention is that all of these patients were examined as regards their basal rate, and it was extraordinary how many of them had a very low basal rate. It is well to bring that up beforehand to facilitate healing. Many patients with high blood pressure will have a fall of blood pressure when put upon thyroid almost to the point of saturation.

Regarding Dr. Baer's reference to weakness of the posterior and anterior vaginal supports, one point is to be noted. As one approaches the vault of the vagina, if one pulls on the lower apices of the marsupialization, he will find that the structures will not descend. It is upon this point that the operation depends.

Barsony, Jenő: Blood Cholesterolin and Ovarian Function, *Monitore ostetrico-ginecologico* 8: 397, 1936.

Barsony found that during pregnancy the cholesterolin of the blood is augmented and increases as pregnancy advances. The oral administration of cholesterolin increases the cholesterolin blood index of normal pregnancy but does not affect the cholesterolin blood index of severe cases of hyperemesis gravidarum. When cholesterolin was administered to mild cases of hyperemesis, cure has always followed. The blood cholesterolin is always increased in cases of fibroids and ovarian cysts. It, however, is diminished following operation, general anesthesia, and traumatic surgery.

AUGUST F. DARO.

Plain or iodoform gauze, soaked in acriflavine in oil, is now packed loosely in both vaginas and is allowed to protrude an inch or two beyond the hymen. A Malecot stay-catheter is placed in the bladder and an artery clamp is put upon it, and the clamp is pinned to an abdominal binder. The clamp is released every three or four hours, the urine drawn off, and the bladder is irrigated once in every twenty-four hours with boracic acid solution, followed by silver nitrate $\frac{1}{8}$ to $\frac{1}{4}$ gr. to the ounce of distilled water. The vaginal gauze is removed about the fourth day, and the bowels are opened between the fifth and seventh days. Douches are not used, and enemas are taboo. Postoperative shock has not been seen, and the post-operative pain is proportionate to the tension one puts upon the sutures closing the perineal skin. Approximation is all that is necessary in skin suturing, suture tension is very discomforting to the patient.

DISCUSSION

DR. LOUIS E. PHANEUF, BOSTON, MASS.—The modification presented adds another operation to the list of vaginal methods which may be employed in the treatment of uterovaginal prolapse. Personally, I have reserved colpectomy for those women who were advanced in years and who felt that sexual relations were not of great importance. In the future I shall be tempted to try the operation devised by Drs. Goodall and Power in the younger group of patients. I feel, that their modification will find a place in the management of large procidentias. The technic, as described, is rather simple, and should offer no particular difficulty to the pelvic surgeon.

The anesthesia which they advocate, namely scopolamine and morphine, and local anesthesia for the perineorrhaphy, is the simplest one could use and is not shocking to old women, who form the largest group for which the operation is recommended. The combination of vaginal hysterectomy and marsupialization allows one to resort to the intervention if, for one reason or another, it is deemed advisable to sacrifice the senile uterus. Loose approximation of the perineal skin, as brought out, is an essential to the patient's comfort.

In my own series, there were 21 subtotal colpectomies or Le Fort operations and 6 total colpectomies, making a total of 27. Amputation of the cervix was done 12 times and perineorrhaphy 26 times. In this group 6 patients were operated upon under local anesthesia, 9 under spinal anesthesia and 12 under general anesthesia. There was no mortality in the series. The result was satisfactory in the 6 total colpectomies and in 19 of the Le Fort operations. There were 2 recurrences in the latter group, giving a percentage of recurrence of 9.5 per cent. The ages of the patients varied from forty-five to seventy-two years.

DR. N. SPROAT HEANEY, CHICAGO, ILL.—The original Le Fort operation leaves the uterus in, and out of the vagina are produced two small passages. The cervix is shut off from observation and the uterus is made difficult of palpation. In the event of a vaginitis it makes a cure almost impossible. Also, in the typical Le Fort operation the pull of the perineal attachment of the vagina to the anterior vaginal wall often produces incontinence of urine.

In brief, I think that an operation that eliminates two-thirds of the Le Fort principle is commendable. With this modification, there is only one-third of the Le Fort operation left and that is the upper third of the vagina with its two passages. I would say that the operation as described is about 66 $\frac{2}{3}$ per cent good, and when Dr. Goodall has eliminated the remaining Le Fort principles the operation will approach 100 per cent in efficiency.

DR. FREDERICK C. HOLDEN, NEW YORK, N. Y.—I am most enthusiastic about the results I have had with the Le Fort operation, and the modification that Dr. Goodall has presented for our consideration is very interesting. Occasionally

it has been our general policy, up to the present, to advise the removal of the tumor when possible as soon as the diagnosis was established, this being also the policy generally advocated in most clinics at the present time. The maternal results have been excellent and no maternal deaths have occurred. This series of cases may be conveniently divided into a number of groups according to the conditions present.

In the first group to mention, there were 7 cases. Operation for the removal of an ovarian tumor was carried out at various periods of pregnancy from two and one-half to five months. In each instance the convalescence was uneventful, and in each instance the pregnancy continued to term. An important point to note in this group is that in no instance was a corpus luteum found in the removed tumor, while in 6 instances it was very definitely observed in the other ovary which was not removed. In one instance there was torsion of the pedicle of the tumor. The type of tumor represented in this group included 2 dermoids, 2 simple unilocular cysts, 2 simple multilocular, and an endometrial cyst. It is interesting to note that the latter presented a striking decidual reaction, as would be expected.

In a second group are included 5 women with parovarian cysts. In four of them operation was carried out during pregnancy at seven and one-half, three months, and in 2 instances at about seven weeks, respectively. Three of them were acute emergencies with torsion of the pedicle of the cyst. In three of these 4 cases convalescence was uneventful and the pregnancy continued to term. In 1 instance however where torsion of the pedicle had occurred, spontaneous abortion occurred the day after operation. This patient, however, had had symptoms of threatened abortion for three weeks prior to operation, and when she aborted, the intact ovum was found to be defective with no visible embryo. In the fifth case the cystic tumor was discovered in the pelvis at the end of the first stage of labor. This presented a possibility of serious trouble, but the tumor was not impacted and the resident in charge, by a stroke of good fortune, was able to dislodge it manually, and spontaneous labor occurred. The tumor was removed by operation in the puerperium, the convalescence being uneventful.

In only 2 instances in our series cesarean section was necessary on account of the mechanical obstruction resulting from the presence of the tumor in the pelvis. One tumor was a dermoid, the other a simple cystoma 10 cm. in diameter. In both instances the tumor was not discovered until late in pregnancy. Elective cesarean section was carried out in each case and the tumor removed at the same time. Convalescence was uneventful in both instances. It is quite possible of course that cesarean section might have proved necessary in some of the women in the first 2 groups had the tumors not been removed earlier in their pregnancies.

On the other hand there were 3 women in our series in whom the pregnancies and labors followed an entirely uneventful course in spite of the presence in each instance of a sizable ovarian tumor. In one the tumor was not discovered until after delivery. This was removed at an elective operation in the late puerperium, and proved to be a dermoid. The convalescence was uneventful. In the other two, the tumors were discovered during pregnancy. Operation was refused, and both patients went to term and were delivered spontaneously. No complications arose during the puerperium.

In another group comprising five patients the interesting association of tubal pregnancy and an ovarian cystoma was noted. It was apparent, however, that the presence of the tumors was not a factor in the causation of the tubal pregnancy. This was evidenced by the fact that 2 of them were lutein cystomas, and probably developed after the tubal pregnancy was established. In a third the tumor, a simple unilocular cystoma, was situated on the side opposite to the tubal pregnancy, while

PREGNANCY COMPLICATED BY OVARIAN AND PAROVARIAN TUMORS*

KARL M. WILSON, M.D., ROCHESTER, N. Y.

(From the Department of Obstetrics and Gynecology of the University of Rochester School of Medicine and Dentistry)

PREGNANCY when complicated by the presence of ovarian or parovarian tumors may at times follow an entirely uneventful course, but on the other hand extremely serious situations may arise which endanger the pregnancy and threaten the life of the patient. In the past, this has been regarded as one of the most serious complications which could occur and in the large series of 720 cases collected by McKerron in 1906, the maternal mortality was 21 per cent while the fetal mortality exceeded 50 per cent. In this series, however, only a few were subjected to laparotomy, most of the women either having had no operation or operation was limited to vaginal puncture of the cyst. Following the application of modern surgical methods to the treatment of this complication the results show a striking improvement and most authorities feel that at present the maternal mortality resulting from this complication should be less than 2 per cent. At the same time it must be recognized that the inherently dangerous potentialities are still present if the condition be overlooked or neglected.

Among the serious possibilities that may develop, the following should be particularly mentioned. Abortion or premature labor may at times occur; the pedicle of the tumor may undergo torsion, giving rise to an acute surgical emergency which may develop during pregnancy or labor, or may occur in the puerperium. Again the tumor may cause serious dystocia, at times being responsible for the occurrence of an abnormal presentation, or offering an insuperable obstacle to the passage of the child through the pelvis. This may necessitate the performance of cesarean section in order to effect delivery, or if the obstacle be not recognized, rupture of the uterus may occur. At times a cystic tumor may rupture during delivery. In the small simple cyst this may be a matter of indifference, but in certain types such as dermoids it may be attended by serious consequences. Occasionally gangrene of the tumor has occurred as the result of prolonged pressure upon it during labor.

The series herewith presented is a small one but it illustrates rather well a number of the possibilities that may occur in connection with this complication. In view of the serious results which may develop,

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had been some slight vaginal bleeding. At operation, a simple cystoma was removed, the corpus luteum was not present in it, but was definitely observed in the other ovary. Pregnancy continued uninterrupted, until eight weeks later when the patient was readmitted on account of profuse bleeding from an imminent abortion which had to be completed artificially. The convalescence was uneventful in both of these patients. The tumors may or may not have been factors in causing the abortions, but this seems rather improbable. In the third patient, a therapeutic abortion with sterilization and removal of an ovarian cystoma was done at the end of the second month of pregnancy. The indication for the operation was found in a serious progressive toxic retinitis. The only reason for including this patient is because the tumor was definitely observed to develop during pregnancy and proved to be a corpus luteum cyst.

DISCUSSION

While obviously no sweeping conclusions can be drawn from such a small series, yet a review of them brings up a number of rather interesting points for discussion. The most serious emergency which developed was to be found in torsion of the pedicle of the tumor. This accident occurred in six or 20 per cent, of our 30 cases. This is a much higher incidence than is seen in connection with such tumors in the nonpregnant individual and represents a real menace to the life of the woman. It undoubtedly is a result of the changing position of the tumor as the uterus enlarges with probably some lengthening of the pedicle, so that the tumor becomes more freely movable within the abdomen, instead of lying more or less protected in the pelvis. While these women represented the most serious emergencies encountered, there were possibilities of serious trouble in the 3 patients mentioned where the tumor offered a mechanical obstruction to delivery, but this was avoided by performing cesarean section on two of them and by a lucky manual displacement of the tumor during labor in the third.

Another point of interest is the fact that in 5 cases the tumor very definitely developed during the course of pregnancy and in each instance proved to be a corpus luteum cystoma. This is a matter of some importance and will be mentioned again in connection with therapy.

That group in which operation included removal of the corpus luteum is of particular physiologic interest. In each instance the operation was followed by abortion. These abortions occurred on the fourth, fifth, tenth, and fourteenth days, respectively, after operation. On account of their time intervals it would seem reasonable to suppose that the patients aborted as a result of the removal of the corpus luteum, rather than from any trauma at operation. As a matter of fact, operation involved little or no handling of the uterus at all. This probability is further supported by the fact that in three of these women, death of the ovum had apparently occurred before the abortion took place. It must be recalled, however, that in one of these patients there had been some symptoms of threatened abortion prior to operation. In this instance the removal of the corpus luteum probably precipitated the abortion.

in the other two, which were simple multilocular cystomas and situated on the same side as the tubal pregnancy, the causative factor of the tubal pregnancy was to be found in a considerable degree of so-called follicular salpingitis. While the tumors apparently played no part in causing the tubal pregnancy, these patients are of interest on account of certain diagnostic difficulties which resulted in some of them. Typical of the mistakes likely to be made would be the diagnosis of the tubal pregnancy and the overlooking of the cyst, or vice versa. In one of our cases the cyst was diagnosed as being associated with a normal uterine pregnancy, tubal pregnancy not being discovered until the time of operation.

Much the most interesting group of patients in this series, from the physiological standpoint, are 5 women who were operated upon during pregnancy, in whom removal of the tumor involved the removal of the corpus luteum. On account of their importance they will be presented in a little more detail.

CASE 1.—(No. 6189.) A thirty-year-old para ii, six or seven weeks pregnant, presenting acute abdominal symptoms in the right lower quadrant together with a cystic mass. Operation revealed a simple cystoma with torsion of its pedicle. The tumor, after its removal, was found to contain the corpus luteum. Spontaneous abortion occurred four days after operation, her further convalescence was uneventful.

CASE 2.—(No. 48333.) A twenty-year-old para i admitted with acute right lower quadrant signs when about six weeks pregnant. An acute appendix was suspected. Operation revealed a simple cystoma, the pedicle not twisted. This tumor after removal was found to contain a recent corpus luteum. Spontaneous abortion ten days after operation, dead ovum. Further convalescence uneventful.

CASE 3.—(No. 34962.) A twenty-five-year-old para i. A left sided cyst, 8 cm. in diameter developed after her first month of pregnancy. At the third month acute torsion of the pedicle occurred. Immediate operation with removal of the tumor which proved to be a corpus luteum cyst. Spontaneous abortion eight days later, dead ovum. Further convalescence uneventful.

CASE 4.—(No. 60685.) A twenty-four-year-old para ii admitted with right lower quadrant pain, six weeks pregnant, diagnosed subacute appendix. At operation removal of an ovarian cystoma which proved to be a corpus luteum cyst. Vaginal bleeding began eleven days after operation, abortion occurring two weeks later. Convalescence thereafter uneventful.

CASE 5.—(No. 45141.) A thirty-two-year-old para 0 admitted on account of some vaginal bleeding and a sensitive mass in the L.L.Q. Ectopic pregnancy suspected. At operation, approximately five weeks pregnant, resection of an ovarian cystoma which proved to be a dermoid but also contained a recent corpus luteum. (There was congenital absence of the opposite ovary.) Spontaneous abortion five days later, dead ovum. Abortion was threatened before operation in this patient and possibly would have occurred in any event.

In our last group in the series are 3 patients, two of whom had spontaneous abortions associated with ovarian cystomas. The first one was admitted on account of severe bleeding from an imminent abortion at about the third month of her pregnancy. The abortion had to be completed artificially. A month later a simple unilocular cystoma was removed, and this was followed by an uneventful convalescence. In the second one, who was about six weeks pregnant, the diagnosis lay between a uterine pregnancy with an associated ovarian cystoma or ectopic pregnancy. There

in whom the corpus luteum was apparently removed in the first month of pregnancy and yet both went to term quite normally.

From what has been said, it is apparent that the corpus luteum and its hormone bear an important relationship to pregnancy. It is also apparent that while in general the corpus luteum is necessary for the proper maintenance of pregnancy in the early months, the duration of the time that this necessity exists varies in individuals. Why this should be so, it is impossible to say, but it offers an interesting problem to speculate upon. Ehrhardt in 1934 and McGinty with his coworkers in 1936 have succeeded in recovering appreciable amounts of progesterin from the human placenta. Quoting the latter, "While the corpus luteum may not be essential for the continuance of human pregnancy, one cannot conclude that the luteal hormone is dispensable from that observation alone since the placenta may produce its own progesterin." If this possibility has any bearing on the situation at all, and one cannot say definitely at present, it again is probably a variable factor both from the standpoint of the time when the placenta acquires the capacity for producing progesterin, and the amount that it produces.

Leaving these more or less theoretical considerations, I will discuss briefly the line of procedure to be followed when an ovarian or parovarian tumor is encountered in association with pregnancy. The situation presents serious possibilities and obviously calls for the surgical removal of the tumor. The operation involved is usually a very simple one and is attended by minimal risk on the part of the patient. The question naturally arises as to when this should be done. If discovered during the early months of pregnancy and removed immediately, the patient is of course relieved of all possibility of serious complications developing later in pregnancy or at the time of labor. On the other hand if removal of the tumor includes removal of the corpus luteum, the probability is that abortion will result. Only occasionally, as in the tumor actually known to have developed during pregnancy, and which probably represents a cystic corpus luteum, will we have any suspicion as to whether the tumor contains the corpus luteum or not. On account of this possibility, one would be rather hesitant about urging operation in the early months, but from this standpoint, there is not sufficient evidence available to say exactly when the period of safety has been reached. I would tentatively place it at about the middle of pregnancy, though recognizing the fact that there are probably many variations from this.

Of course in the presence of an acute emergency such as torsion of the pedicle, immediate operation is indicated no matter what the period of pregnancy. In the event that operation involves removal of the corpus luteum, I would offer as a therapeutic suggestion, that the immediate administration of progesterone be begun. I have not had the

The question naturally arises as to how long the corpus luteum and its hormone, progesterone, are essential for the maintenance of pregnancy in the human female. Unfortunately our present state of knowledge does not permit a specific answer to this question. Many observations by a number of investigators have given us a clear idea as to the relationship of the corpus luteum and its hormone, progesterone, to pregnancy in the experimental animals. Thus, Fränkel's pioneer work showed that removal or destruction of the corpus luteum in the first half of pregnancy in the rabbit resulted in either death of the embryos with resorption or abortion. Allen and Corner succeeded in maintaining pregnancy to term by the administration of corpus luteum hormone in rabbits which were castrated immediately after mating. Snyder has brought about the prolongation of pregnancy in the rabbit by inducing a second ovulation with the development of new corpora lutea in the latter part of pregnancy. From such experiments it is obvious that the corpus luteum and its hormone have a profound influence on pregnancy in this species of animal. In the guinea pig, the removal of the corpora lutea during pregnancy generally results in abortion, but not always, and even when removed in the first half of pregnancy at times no interruption to the pregnancy results.

In the woman, observations at the time of cesarean section at term will in many instances reveal the corpus luteum of that pregnancy as still being present, while in others it cannot be seen and presumably has degenerated some time previously. I have observed similar variations in abdominal hysterotomies at earlier periods of pregnancy, when therapeutic abortion and sterilization was indicated, though not in the first three months. The woman who habitually aborts, presumably aborts on account of premature degeneration of the corpus luteum, and many of these women can be carried through pregnancy successfully by the administration of progesterone for the proper period of time, but it is usually not necessary to continue the therapy to term.

In the 5 patients noted in our series above, all aborted after the removal of the corpus luteum in early pregnancy. This is a common experience and has been noted by many authors. In 2 cases reported by De Lee in 1916 an attempt was made to maintain the pregnancy by transplanting the corpus luteum after its removal, but without success. When abortion does occur after the removal of the corpus luteum, there seems to be little or no doubt that this is the primary causative factor.

On the other hand, this may not be the inevitable result. Thus Ask-Upmark, in a collected series includes 17 examples where bilateral oophorectomy was performed during early pregnancy and yet the pregnancy continued to term. In three of these, the pregnancies were in the first month. In these the corpus luteum obviously must have been removed at the time of operation. More recently, Pratt reported 2 patients

A near tragedy once resulted from my failure to recognize at the time of my original examination that a patient had an ovarian cyst in the midline in front of the uterus. This patient consulted me first on Feb. 20, 1928 stating that her last period had occurred on December 11. At the time of this first examination I found what was believed to be an evenly enlarged uterus the size of a four months' pregnancy. On April 4 she developed a severe right-sided pain, which proved to be due to pyelitis, and on April 27 the uterus was emptied by vaginal hysterotomy. While the mass believed to be the uterus remained too large following the termination of pregnancy her general condition seemed better, and she was permitted to go home. About a week later, however, she was brought back to the hospital with abdominal pain and vomiting, and it was evident that she had an acute abdomen with intestinal obstruction. On opening the abdomen a gangrenous right-sided ovarian tumor 12 by 16 cm. in diameter presented itself. There were several twists of the pedicle and this involved the appendix which was also gangrenous. The tumor and appendix were removed without difficulty. I next explored the culdesac and found a gangrenous loop of intestine. Twenty-five centimeters of the ileum were removed and a lateral anastomosis made. Examination of the specimen indicated that the patient had an old dermoid cyst which had rotated so as to lie on top of the pregnant uterus.

Fortunately the patient made an uneventful recovery and became pregnant again in May, 1930. When examined shortly after missing the first period, a left-sided cyst about 8 cm. in diameter was found. This began to show evidence of a reduction in size near the end of the first trimester, and following delivery, examination indicated that the left ovary was only moderately larger than normal. There was no evidence of cyst formation during a third pregnancy which occurred in January, 1932.

DR. J. L. FRAENKEL, NEW YORK, N. Y.—We are badly in need of a collective study of the comparative physiology of the corpus luteum in all mammals. My scientific friends and pupils, headed by my old assistant Fels, are at work upon this comparative study. In my trip around the world I won many coworkers, each one investigating one animal, from the marsupials in Australia to the viviparous snakes in São Paulo.

DR. HARVEY B. MATTHEWS, BROOKLYN, N. Y.—I wish to report a short series of cases from the Methodist Episcopal Hospital. There were 11 complicating ovarian cysts in the last 8,500 deliveries. Delivery was 6 times by cesarean section. Four patients were delivered from below without trouble, the cyst having slipped spontaneously out of the way either before or during labor, or we were able to displace the cyst. One patient who was five months pregnant was operated upon for an ovarian cyst with a twisted pedicle, and later hysterotomy was done for a dead fetus. Another patient was operated upon when four months pregnant for ovarian cyst with a twisted pedicle and was subsequently delivered at term without trouble.

The x-ray helps a great deal in diagnosis. A young woman, thirty years old, was sent to me for operation for an ovarian cyst. On examination I decided it was not an ovarian cyst but a pregnancy of about four months' duration in a thin-walled symmetrical uterus. X-ray demonstrated the fetal bones, although the patient refused to accept the diagnosis. If a dermoid cyst or a pregnancy is suspected there is no better way to make the differential diagnosis than with the x-ray, provided of course the duration of the pregnancy is sixteen weeks or more.

DR. CLARENCE B. INGRAHAM, DENVER, COLO.—I have encountered 13 cases of ovarian tumor during pregnancy. Five were pseudomucinous cystadenomas. Two of these were very large, one being found ruptured postpartum. There were four simple cysts, one parovarian cyst with a twisted pedicle, one serous cystadenoma,

opportunity as yet of carrying out such therapy since progesterone became available, but it would appear to be a logical form of therapy to employ.

In the second half of pregnancy operation should be attended by little risk either to the pregnancy or the patient. If, however, the tumor is not discovered or if the patient is not seen until the last month of pregnancy, in most instances the procedure of choice will be to perform cesarean section and at the same time remove the tumor. If the tumor has resulted in a mechanical obstruction at the time of labor, this will of course be the obvious procedure to follow. Finally if the tumor for one reason or another not be removed during pregnancy, operation should be carried out as early in the puerperium as is possible.

SUMMARY AND CONCLUSIONS

Thirty patients with ovarian and parovarian tumors associated with pregnancy are presented. All but two were operated upon with no maternal deaths. In 5 women, where removal of the tumor involved removal of the corpus luteum, abortion occurred in each instance. Abortion occurred in 3 other instances but the accident was apparently not attributable either to the tumor or the operation.

Torsion of the pedicle of the tumor was found to be a frequent complication, occurring in 20 per cent of the patients in the series.

A tumor known to develop during the course of a pregnancy will quite probably prove to be a corpus luteum cystoma.

Suggestions as to the modification of the rules of treatment are presented.

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DISCUSSION

DR. CARL H. DAVIS, WILMINGTON, DELAWARE.—Dr. Wilson's experience confirms earlier observations regarding the risk to the pregnancy from too early removal of a cyst developing in the ovary containing the corpus luteum of pregnancy. Obviously acute symptoms from torsion may necessitate prompt surgical removal, but when possible the operation should be postponed until the second trimester is well started. Besides the lessened risk to the pregnancy a considerable percentage of the cysts up to 3 or 4 inches in diameter are temporary corpus luteum cysts which gradually disappear after the first trimester.

The problems associated with diagnosis have caused me greater concern than the question of treatment after a definite diagnosis. A small corpus luteum cyst associated with spotting may be found during the first trimester and one may be uncertain as to whether the patient has an intrauterine or extrauterine pregnancy.

My first experience with ovarian tumors occurred about 1901. The patient had a cyst of the left ovary larger than the fetal head which had prolapsed into the pelvis, and one of the right ovary the size of a grapefruit. She had been in labor much over twenty-four hours, attended by two general practitioners who were hoping that the tumor would recede, permitting the head to descend. A cesarean section was performed and then both tumors and the tubes were removed. Much to my surprise over a year later I performed a second section, and later the patient had still a third section. It is evident that some of the ovarian cortex must have been left.

When it was believed that the corpus luteum of pregnancy played a vital rôle in preserving the pregnancy, I was accustomed to shell out the corpus luteum if it were in the ovarian tumor and merely drop it into the abdomen. By good fortune or coincidence none of my patients whose tumors were removed early in pregnancy aborted. Such procedure, or the burying of the corpus luteum, should not be done in the event that a papillomatous or ovarian dermoid carries the corpus luteum. Possibly the luteal extracts now on the market may obviate the necessity of considering the retention of the corpus luteum in the event its development were in the tumor.

DR. J. P. PRATT, DETROIT, MICH.—May I say a word about assuming too readily that the corpus luteum is responsible for the prevention of abortion. Several of the patients described had sufficient difficulty before operation to threaten abortion. Some pregnant patients in whom a laparotomy is performed, a gallbladder and appendix or nothing at all is removed, abort following the operation. This certainly does not indicate that the loss of the gallbladder or appendix causes abortion.

Much of our present opinion concerning the progestin mechanism in the human being is a matter of inference from animal experiments. The need for the corpus luteum hormone may not be so great in the human being as would be inferred from animal work.

In one instance I removed a corpus luteum on the twenty-first day after the onset of the last menstruation. The patient had come for sterility, and was operated upon for retroversion and other complicating circumstances. It seemed safe on account of the recent menstruation to remove the corpus luteum for study. The patient did not menstruate in the usual two or three days following the removal of the corpus luteum but continued through a normal pregnancy and lactation. This is, therefore, one clear-cut illustration of a normal pregnancy without the presence of a corpus luteum after the beginning of nidation. Both ovaries had been carefully inspected to insure that no other corpus luteum was present.

DR. WILSON (closing).—Of course, in comparing the conditions in human beings and in animals we get in trouble right away as the time relationships are quite different. In the rabbit, for instance, the pregnancy lasts only thirty days. Destruction of the corpus luteum in the first half of the pregnancy terminates the pregnancy. Of course the rabbit is a very immature animal at birth, and we cannot say that fifteen days of the pregnancy, or half its duration corresponds to a similar time in the woman's pregnancy.

In regard to the therapy I hope sometime to have the opportunity, in a case of torsion of a cyst for instance, with removal of the corpus luteum, of following the operation by the administration of progesterone.

20 pounds in weight and one dermoid. Finally there was a case with a graafian follicle cyst and corpus luteum in the same ovary, included in this group because abortion followed its removal.

Four abortions occurred within the first two months of gestation and two later miscarriages. One abortion occurred prior to the finding of the cyst. The patient with the graafian follicle cyst and corpus luteum in the same ovary was operated upon as an ectopic pregnancy on account of bleeding. Another patient with a corpus luteum removed on the same side as the cyst, two months pregnant, aborted three days after her operation.

Early in pregnancy the lutein-like substance from the placenta may take care of the pregnancy. Petri mentions the case of Essen-Möller who extirpated both ovaries with the corpus luteum, but delivery at term followed 260 days after operation.

I believe it is the consensus of opinion that operation for removal of the tumor is best done after the second month and during the first half of pregnancy. Though operative technic has improved since the time of McKerron's report, I believe his findings are still representative:

MONTH OF PREGNANCY

ABORTIONS EXCLUDING COMPLICATIONS

2	5----18.5%
3	5---- 8.8%
4	3---- 5.3%
5	2---- 6.2%
6	4----22.2%
7	3----20.0%
8	4----57.1%
9	0----00.0%

These figures show that most miscarriages follow operations done in the second half of pregnancy. In the last month of pregnancy, removal of the cyst with cesarean section is indicated, for we would not want a patient to go into labor immediately following an abdominal operation.

DR. JOSEPH B. DE LEE, CHICAGO, ILL.—Years ago when the theory that the corpus luteum preserved pregnancy was first advanced, I applied this principle in two cases. Both patients had ovarian cysts, one being about two and one-half months pregnant and the other not quite four months. The corpus luteum in each case was in the ovary which I had to remove, so I cut out the corpus luteum, split it and planted it in the folds of the broad ligament, hoping thus to prevent an abortion. This had never been done before and not to my knowledge since that time. The results were not happy. One woman aborted within several days. In the other abortion began several hours after the operation, but when I started to clean out the uterus I found it had ballooned out to the size of a six and one-half months' pregnancy and was above the navel. There was an acute paralysis of the uterine wall and the uterus was full of blood.

Paralysis of the uterine wall is not an unknown entity. Buettner of Basel, Switzerland, reported several cases of acute dilatation of the uterus in pregnancy, and it is possible that we might associate this action of the transplanted corpus luteum in this case with the modern theory that it produces a hormone which relaxes the uterus.

DR. RUDOLPH W. HOLMES, CHICAGO, ILL.—In my own experience I had to deal with far more tumors complicating pregnancy during the first half of my practice than in the later years. This difference I have ascribed to the fact that gynecologists have eliminated those ovarian tumors antedating pregnancy by operation.

neoplasms could assume a great variety of forms so that nothing approaching a classification of them was possible until 1915 when Robert Meyer published his monograph on the subject. However, in 1931, Moulouguet and Dobkevitch published the work of their teacher, Leeéne, who apparently had long before recognized a luteinized type of granulosa cell tumor, had collected and studied several specimens, and had named them "folliculome lipidique." It was not until 1932 that the last member of this interesting group of tumors was reported by Loeffler and Priesel to which they gave the name of "fibroma theca cellulare xanthomatodes ovarii," more commonly known as the theca cell tumor.

Thus the discovery and collection of data concerning this family of neoplasms have already covered many years. There still remains much to be done, as the lutein tumors and theca tumors are somewhat rare. However, a great step has been taken to shorten the process, for Furth and Butterworth have discovered a method whereby the granulosa and lutein tumors can be produced in large numbers in the experimental animal. In a series of studies on experimentally induced leucemia, they discovered that a considerable percentage of their radiated mice developed these ovarian tumors. This abundant source of material makes it possible to examine more completely all stages of growth and to determine more accurately interrelationships between them, as well as to study their origins.

It is the purpose of this paper to summarize our knowledge of the human tumors in some detail and to draw conclusions concerning them through comparison with what has been observed in the mouse tumors.

CLINICAL DATA CONCERNING THE HUMAN TUMORS

The theca cell tumors would seem to be somewhat rare, as only about twenty-three such tumors have been reported. However, they are probably of much more frequent occurrence than this would indicate for, as will be noted when their histology is discussed, they are difficult of recognition, particularly in the unluteinized (undifferentiated) forms. Granulosa cell tumors are much more common. Schröder estimates that they constitute from 2 to 3 per cent of all solid ovarian tumors, while Von Szathmary found 9 in a series of 203 solid tumors, or an incidence of 4.4 per cent. The luteoma, like the thecoma, is also a rare tumor because, though easily recognized, only twelve have been recorded in the literature. However, partially luteinized granulosa cell tumors are much more common. The age incidence can be given with some degree of definiteness with regard to the granulosa tumors. They are most commonly found in women over forty years of age, although occasional examples are seen in younger women between puberty and the menopause, and a few in children. The luteomas were all seen in mature women ranging from twenty-one years to sixty-five years of age, while all excepting four of the thecomas have been found beyond the menopause.

THE THECA, GRANULOSA, LUTEIN CELL TUMORS OF THE HUMAN OVARY AND SIMILAR TUMORS OF THE MOUSE'S OVARY*

HERBERT F. TRAUT, M.D., AND J. S. BUTTERWORTH, M.M.,
NEW YORK, N. Y.

(From the Department of Obstetrics and Gynecology, and the Department of Pathology, Cornell University Medical College and New York Hospital)

THE process of accumulating knowledge concerning neoplastic growths falls quite naturally into different phases. Among these the most important are the clinical description of patients harboring the growth, the histologic study of the tumor, investigation of its embryologic background, physiologic studies of it, and finally, its biologic evaluation. Studied in these various ways, tumors yield many of the important facts which the physician must possess. However, it is rarely possible to apply all these methods of attack to a given type of tumor or group of tumors, either because we do not know how to apply them or because the tissues in question do not adapt themselves to one or another of the modes of study. In the theca, granulosa, lutein cell group of neoplasms, we have an unusual opportunity to acquire information, because all the procedures mentioned are applicable. These tumors present definite clinical evidence of their presence by the symptoms they produce; their histologic aspects are characteristic; study of their embryologic background yields most helpful information; they are physiologically active because they secrete hormones which influence other tissue in ways we can evaluate; and finally, we have learned how to produce them in a laboratory animal so that they may be studied not only in every phase of development, but also as frequently as we desire. Therefore, this group of tumors presents an unusually fertile field for study and one in which great strides toward understanding have been made.

A study of the literature concerning these tumors indicates that the first contribution was made by Rokitsansky in 1859 when he described a lobulated tumor the size of a child's head in the left ovary of a woman aged sixty-five. This tumor was composed entirely of lutein cells containing much lipid material. A little later, in 1882, Maffucci recorded the details of a similar tumor, excepting that the lutein cells were not so predominant, there being granulosa cells as well as theca cells present in large numbers.

Von Kahlden, in 1895, gave the first unmistakable description of a granulosa cell tumor and named it "graafian follicle adenoma." This announcement of a new type of tumor attracted wide attention, so that in the years following, many other granulosa tumors were recognized and described. It was soon learned that these

*Read at a meeting of the Brooklyn Gynecological Society, April 2, 1937.

and then subsequently stimulate the growth of granulosa cells to such a degree that tumor formation results. It is interesting to note reports in the literature of a number of patients who developed granulosa cell tumors following heavy radiation. The cases of Vogt, Smith, and an unpublished case at the Memorial Hospital are examples of this type of reaction in the woman.

HORMONAL EFFECTS OF THE THECA, GRANULOSA, AND LUTEIN CELL TUMORS

As has been mentioned, the predominant effect of these tumors so far as we are now able to judge is upon the uterus and breast, with some influence upon the secondary sex characteristics. This seems to be due to the secretion of estrin, because prolonged injection of large amounts of estrin in the experimental animal can be shown to produce exactly analogous phenomena in the uterus and its endometrium.

However, very exceptionally, so-called granulosa cell tumors may be associated with a secretory (premenstrual) type of endometrium. It would seem probable, therefore, that occasionally some luteinization takes place in such cases, so that progesterin also becomes a product of the tumor (folliculome lipidique of Lecène). Biologic proof of this deduction is lacking, so that it is based only upon histologic evidence and must, therefore, be viewed with reserve.

The effect of luteomas on the endometrium is obscure because only a few tumors of this type have been reported, and none has been described specifically as to its effect on the endometrium. The clinical histories, however, speak chiefly of an amenorrhea with the exception of Wolfe's case, a young woman of twenty-one years, who showed menstrual irregularity. As we shall see in the mouse luteomas, the effect on the endometrium is mainly a proliferative one, only occasional secretory activity having been induced.

Curiously enough, one seldom sees fibromyomas of the uterus or chronic cystic mastitis associated with the hyperestrinism induced by granulosa cell tumors. If the theories of Witherspoon and those of Geschiekter and Lewis be true, one might expect to find some increased evidence of these pathologic conditions associated with granulosa or theca cell tumors, especially in the premenopausal group of patients.

The secondary sex characteristics usually are predominantly feminine in patients harboring one of these tumors, and as has been noted, they may be called forth prematurely in the young. However, a few instances of masculinization are to be noted as exceptions, such as the case of luteoma reported by Cosaresco, and an unreported case of granulosa cell tumor in Studdiford's experience. In these patients, masculine hair distribution, excessive beard growth, coarsening of the facial features, deepening of the voice, amenorrhea, and penile hypertrophy of the clitoris were seen. Clinically a preoperative diagnosis of arrhenoblastoma was justifiable in these patients, and yet the tumor

SYMPTOMATOLOGY

The clinical history of patients having one of these tumors depends primarily upon the fact that they possess endocrine activity, while mechanical and circulatory disturbances, and occasional malignancy, are accessory factors. The hypersecretion of estrin by the theca, granulosa, and probably also by the lutein cell tumors produces a characteristic syndrome associated with hyperplasia of the endometrium, irregular uterine bleeding and gradual symmetrical hypertrophy of the musculature of the uterus. In the prepubertal female, luteomas and thecomas do not occur; therefore, precocious development of the secondary sex characters and uterine bleeding are seen associated only with the granulosa tumor, or with tumors outside the ovary, such as those of the adrenal and prepituitary gland.

After the menopause there is a recurrence of a more or less regular type of uterine bleeding, enlargement of the atrophic uterus and occasionally a recrudescence of sex desire. Infrequently breast atrophy is replaced by transitory hyperplasia. Curettage of the uterus reveals a cystic glandular hyperplasia of the endometrium in the majority of patients; however, a few instances have been reported in which the premenstrual or secretory type of endometrium was seen, even in women of advanced age.

During the period of sexual activity, the symptomatology due to the endocrinal potencies of the tumors is less noticeable because of the proximity of normal menstrual function and also because the other ovary which is often normal may serve to mask the picture. However, there is usually a period of amenorrhea followed by menorrhagia or metrorrhagia, or there may be simply irregularity of the menses.

If the tumor is benign, its removal serves to reestablish the former status of the patient, thus giving clinical proof of its endocrinal activity, excepting that in those prepubertal cases where the menarche is imminent, the individual may continue sexual development with more or less normal periodicity of the menstrual function.

Approximately 80 per cent of the granulosa tumors are clinically benign. When malignant, they metastasize rapidly and produce death in a short time. Only one case of malignant theca cell tumor has been reported, while the luteomas are probably more frequently in this category, as three of the twelve tumors reported have been interpreted in this way.

Nothing is known concerning the radiosensitivity of thecomas and luteomas. Although, judging from the effects of radiation upon the normal theca and lutein cells of the mouse, it would seem that they were most radio-resistant. All observers with few exceptions agree that the malignant granulosa cells are extremely sensitive to radiation therapy. As we shall show in the mouse's ovary, x-rays at first depress

Mitoses are not seen. They tend to differentiate from the mesenchymal type of connective tissue cell in an epithelial direction. In doing this, they retain the intracellular collagen fibrils but tend to increase in size slightly and develop an increased tendency to stain with fat stains because of the appearance of cholesterol esters within the cells. This change presumably is somewhat analogous to the change seen in some granulosa cell tumors when they undergo luteinization. There are, therefore, two distinct types of theca cells with regard to the degree of differentiation: the luteinized, which form is easily recognized because these cells stand out clearly from the connective tissue background; and the unluteinized, which is more difficult of recognition, and in all probability is not identified histologically in its true relationship by the majority of pathologists.

The granulosa cell tumors offer much less difficulty in diagnosis than the thecomas, because they are far better known. However, they assume such a variety of cell arrangements, as well as different degrees of cellular differentiation, that some space should be devoted to a detailed description of them.

The granulosa cells, themselves, resemble the cells lining the normal graafian follicle. They have a small oval or round nucleus which takes the hematoxylin and other basic stains intensely. This is surrounded by a scanty cytoplasm which is very faintly acidophilic. The cells are uniform in size; their shape, however, varies with their environment, assuming almost any form necessary for accommodation to a given space. They vary also with their degree of differentiation from cells such as those seen in the primordial graafian follicle to the hypertrophic, pale and fat laden cell seen in the lutein stage. In the latter phase, the cells contain phospholipoids and respond to specific fat stains. Call-Exner bodies consisting of a radiating rosette of granulosa cells about a small acinus, the latter containing hyalinized fragments of cellular debris, are often seen and are quite pathognomonic when present. Aside from the variations in the cells themselves, groups of cells show marked versatility in the patterns they describe. The following constitute the most striking types of organization:

1. Folliculoid arrangement of the cells into small or large acini surrounded by a margin of granulosa cells resembling in some degree at least the normal graafian follicle, is the most common and probably represents the best differentiated form of the tumor. The theca interna may be scant or absent. The central cavity contains liquor folliculi into which, not infrequently, hemorrhage has taken place.

2. Other tumors display a cylindromatous arrangement of dense columns of cells separated by fibrous connective tissue. There is little or no cyst formation. This may be considered a less differentiated form of the tumor than the folliculoma. When partial luteinization has occurred, and particularly when the columns of cells are widely separated by connective tissue stroma, these tumors have been mistaken histologically for Brenner tumors until specific stains were applied to distinguish the fundamental difference in the nature of the cells.

of the ovary in each case showed respectively a luteoma and a granulosa cell tumor. The hormonology of these aberrant cases is not clear at the present time, but it seems quite probable that there may have been some adenomatous elements of the adrenal cortex in the ovarian tumors or the adrenal gland itself.

PROOF OF HORMONAL ACTIVITY

Siebke and Sehuschiana, Frank, Pahl, Neuman, Melnick and Kanter, and Spielman have presented a convincing mass of experimental proof that the blood of patients with granulosa cell and theca cell tumors contains increased amounts of estrin. Furthermore, it has been shown that the tumors themselves, and particularly the thecoma, contain the substance in large amounts. The investigations seem to indicate that, although these tumors do not excrete excessively large amounts of estrin, the secondary hormonal effects are in all probability produced by its long-continued and constant action, on the one hand; and on the other, that there is no opposed corpus luteum effect in most cases. Further studies along these lines are much needed, particularly in connection with the luteinized types of granulosa tumors such as described by Maffucci, Plate and Lec  ne, and also the true luteoma.

HISTOLOGIC ASPECTS

The gross pathologic characteristics of these tumors are so varied as to defy description. However, in general it may be said that the thecomas tend to simulate fibromas of the ovary in size, shape, and consistency. The cut surface also bears out this resemblance with the exception that the white fibrous whorls of tissue may be flecked or streaked with yellowish areas. This color is due to the carotin contained in the theca cells.

The granulosa tumors are more versatile in their gross manifestations. They may be smooth or lobulated in surface contour and are frequently semisolid or cystic; cyst formation depends upon the type of tumor differentiation, the folliculomas being more soft and cystic than other forms. The larger tumors tend to necrosis so they may be quite soft and contain degenerative cyst cavities. The coloration of the cut surface is yellowish gray with a marked frequency of hemorrhagic discoloration of the cystic areas. About 10 per cent are bilateral. The luteomas are more often solid than cystic and are not noted as being of large size. Their cut surfaces display a homogeneous yellow matrix of cellular tissue.

Theca tumors appear microscopically as fibromas in which islands of fusiform cells occur. These cells are arranged in a basket weave pattern and are characterized by the intracellular fibrils which serve to differentiate them from the ordinary ovarian stroma cell. They are possessed of an elongated nucleus which is quite uniform in size.

of the lutein cells to the blood vessels is a very intimate one in which the cells are often seen to be grouped about the blood vessel in a definite perivascular arrangement. Fat stains show the clear cells to be heavily laden with fat droplets.

HISTOGENESIS OF THE THECA, GRANULOSA AND LUTEIN CELL TUMORS

Our knowledge of the antecedent cells from which these tumors are derived is somewhat incomplete. Due to the difficulties surrounding

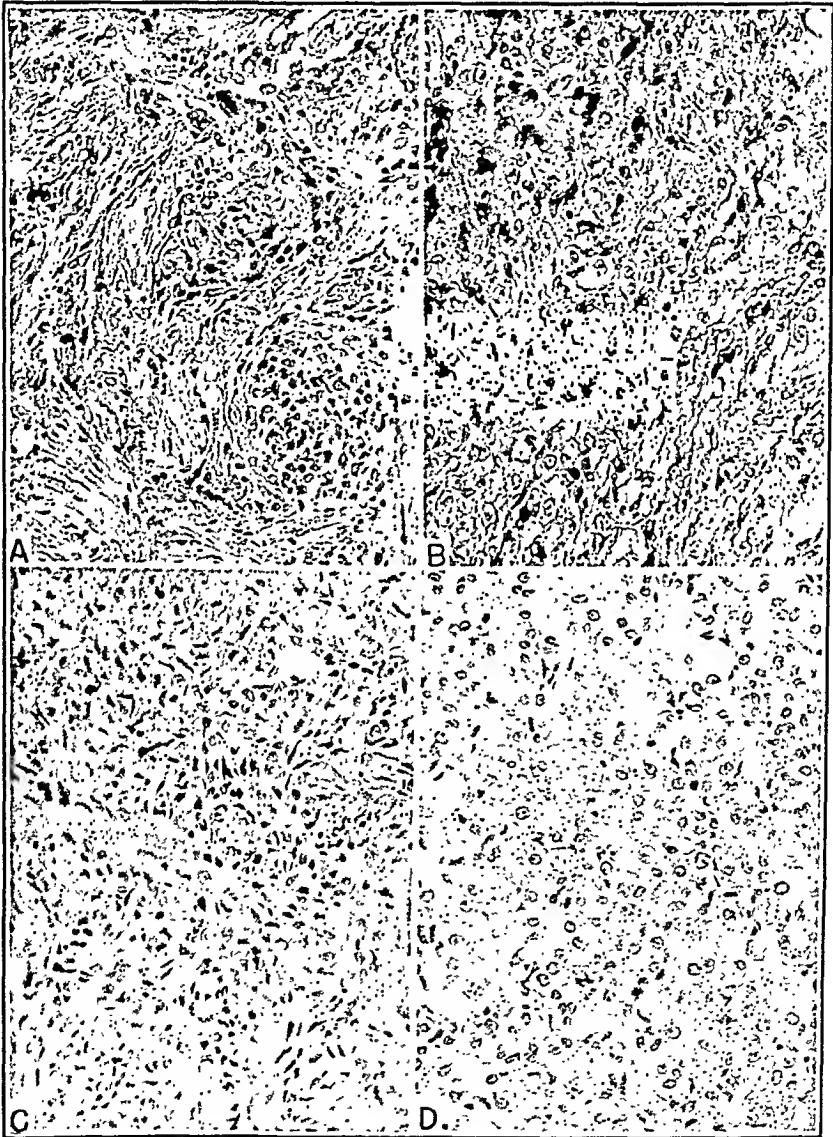


Fig. 1.—Theca tumors. *A*, Thecoma of mouse's ovary showing only moderate differentiation and no luteinization. *B*, A better differentiated tumor from human ovary showing a few luteinized cells. *C*, A human theca cell tumor with an even representation of luteinized and unluteinized cells. *D*, Complete luteinization in a human thecoma.

the absolute identification of cells in the embryonic ovary, as well as the complexity of the cytologic changes taking place in rapid succession, some differences of opinion and misconception have arisen. For many years following the teachings of Pflüger (1863) and Waldeyer (1870),

3. Still other tumors show a tendency on the part of the granulosa elements to dispose themselves between planes of connective tissue forming tongue-like processes or trabeculae, seldom growing into solid sheets or cylinders of cells. This is usually a diffuse sort of growth and is the least differentiated pattern, although the cells, themselves, may appear to be quite adult and well formed.

4. Rarely the granulosa cells form a system of tubules in which single rows of cells arrange themselves about a central acinus as though it were a duct. Such an arrangement of cells might be thought to be related to some form of tubular adenoma, such as Pick's testicular tumor, were it not that one can usually prove beyond doubt that they are true granulosa cells.

The connective tissue elements, particularly in the trabecular forms, are very vascular. In the follicular variety the connective tissue yields a basement membrane which at times closely resembles theca interna, but for the most part is compressed and partially or completely hyalinized. Occasionally fibrous connective tissue forms the bulk of the tumor with only scant infiltration or small isolated areas of granulosa cell development.

Not infrequently one finds several of the above varieties of arrangement of the granulosa and connective tissue in different portions of the same tumor, indicating presumably different stages of growth or of differentiation.

Apparently any variety of granulosa cell tumor and many theca cell tumors undergo luteinization. Attention to this somewhat uncommon finding was first directed by the teachings of Lecéne who, in the case of the granulosa tumor, gave it the name of "folliculome lipidique." This change is accompanied by a loss of the dense basophilia characteristic of the granulosa cell tumor, some increase in the size of the cell and shrinkage of the nucleus. These cells and the connective tissue about them contain phospholipoids and consequently take the various fat stains quite densely.

Whether a human granulosa cell tumor can become completely luteinized to form a luteoma remains an open question. That this occurs in a mouse tumor there can be no doubt, as will be described presently. However, several partially luteinized tumors such as those described by Lecéne have been reported.

The luteoma, therefore, may develop *de novo* from other lutein cells, as has been believed. However, this seems unlikely, because mitoses and other evidences of young lutein cells are rare in these tumors. The lutein cells are usually quite uniform in size and have a clear "ground glass" type of cytoplasm which stains only slightly with acid stains. The cytoplasm is abundant with definite cell outline, showing a "mosaic" or "flagstone" pattern. The nucleus is small and eccentrically placed. In several tumors small cells have been described which have a more opaque and slightly basophilic cytoplasm as well as a larger nucleus. It would seem that these are granulosa cells which have not completely undergone the lutein change. The relationship

formation of the graafian follicle. The primordial sex cells are thought to be derived from coelomic epithelium at some distance from the gonad and to migrate into it during early fetal life. After the arrival of the sex cells, and under their influence, the primitive mesenchymal stroma of the ovary undergoes a series of changes which surrounds each sex cell with an envelope of primitive granulosa and theca cells.

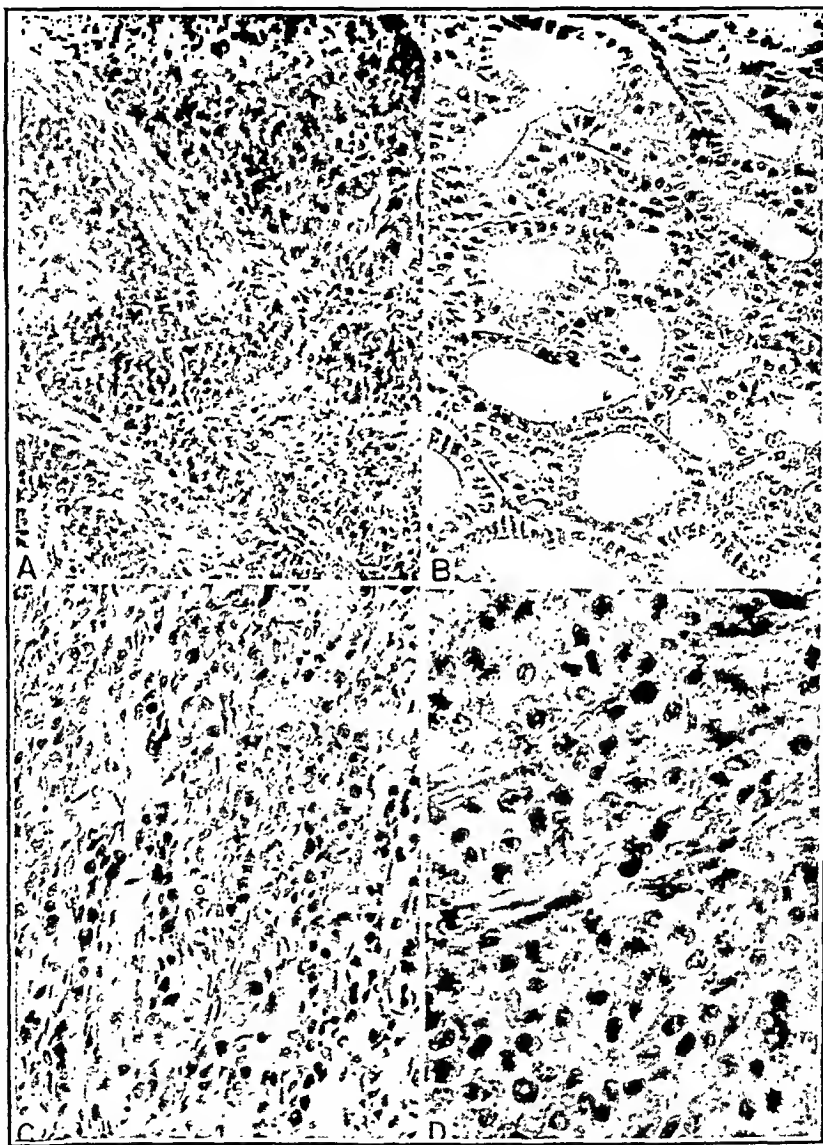


Fig. 3.—Granulosa tumors of the human ovary. *A*, Trabecular arrangement. A common picture in rapidly growing tumors. *B*, Tubular arrangement, which is quite rare. Unquestionably granulosa, but simulating Pick's tubular adenoma. *C*, Sarcomatoid arrangement. Benign, but with few granulosa cells scattered among the connective tissue stroma cells. Patient alive and well six years after operation. *D*, Granulosa cell carcinoma, malignant. Note mitotic figures. Patient died with metastases from this tumor, three months after operation.

If the Fischel concept be true, then the tumors of the granulosa series with their varied cellular content and pattern are mesenchymal instead of mesodermal in origin and are, therefore, more readily understandable.

it was thought that the granulosa as well as the primitive ova were derived from the coelomic epithelium covering the surface of the ovary. A process of down growth of this epithelium in cords to form the so-called Pflüger tubules has been described by many students of the fetal ovary. That at times there are proliferations of the germinal epithelium to support such a theory seems undoubted. However, more



Fig. 2.—Granulosa tumors of human ovary. A, Typical "folliculoma" arrangement: each acinus is lined by granulosa cells, and contains liquor folliculi and often some blood cells. B, A solid arrangement with many small follicles, the small ones being "Call and Exner" bodies. This is less well differentiated than the "folliculoma." C, Cylindroma arrangement. Still less differentiated. Solid columns of cells split up by connective tissue septa. D, An unusual cylindroma showing early lutein change, simulating a Brenner tumor.

recently, principally through the influence of the Viennese embryologists, under Fischel's guidance, a different explanation of the origin of the theca, granulosa, and ova has come to be understood and at least partially accepted. According to the Fischel school, it now seems very probable that the germinal epithelium contributes nothing to the